Computational modelling of mycobacterium infection and innate immune response in zebrafish

Viana de Carvalho, R.

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Appendix A

A Petri net is represented by a directed, finite, bipartite graph, typically without isolated nodes. The three main components are: places, transitions and arcs. In addition, there are markings describing global states. Basically, places and transitions alternate on a path connected by consecutive arcs. In this appendix, we provide a formal definition of the Qualitative Petri net method as used for the model presented in Chapter 3.

Qualitative Petri nets (QPN): Formal definition

Based on [10] we define a Qualitative Petri net as tuple $N = (P, T, A, I)$, where

- P is a finite nonempty set of places;
- T is a finite nonempty set of transitions such that

$$P \cap T = \emptyset. \tag{A1}$$

- A is a finite set of arcs, weighted by non-negative integer values such that

$$A \subseteq (P \times T) \cup (T \times P) \to \mathbb{N}. \tag{A2}$$

- I is an initialization function (the initial marking) such that

$$I: P \to \mathbb{N}. \tag{A3}$$

Appendix B

A stochastic Petri net is an extension of the Petri net formalism in which random firing delays are associated with transitions whose firing is an atomic operation. The specification of the firing delay is of probabilistic nature, i.e. probability density function or probability distribution function. This appendix provides a formal description of the Stochastic Petri net method as used in Chapter 5.

Stochastic Petri nets (SPN): Formal definition

Adapted from [53] we define a Stochastic Petri net as tuple $N = (P, T_U, A, V, I)$, where

- P is a finite nonempty set of places;
- T_U is the union of two disjunctive transition sets

$$T_U = T_{stoch} \cup T_{im}. \tag{B1}$$

  where :

  1. T_{stoch} is the set of stochastic transitions with exponentially distributed waiting time
  2. T_{im} is the set of immediate transitions with waiting time zero

- A is a finite set of arcs, weighted by non-negative integer values (cf. A2)
- V is a function such that

$$T_{stoch} \rightarrow H \tag{B2}$$

  which assigns a stochastic hazard function h_t to each transition t, whereby

$$H = \bigcup_{t \in T_{stoch}} \{h_t | h_t : \mathbb{N}^{|{}^\circ t|} \rightarrow \mathbb{R}^+\} \tag{B3}$$

  is the set of all stochastic hazard functions, and

$$V(t) = h_t \; \forall \; t \in T_{stoch} \tag{B4}$$

- I is an initialization function (the initial marking) (cf. A3)

The stochastic hazard function h_t defines the marking-dependent transition rate $\omega_t(m)$ for the transition t, i.e. $h_t = \omega_t(m)$. The domain of h_t is restricted to the set of input places of t, denoted by ${}^\circ t$ with ${}^\circ t = \{p \in P | A(p,t) \neq 0\}$, to enforce a close relation between network structure and hazard functions. Therefore, $\omega_t(m)$ actually depends on a sub-marking only.

Appendix C

Colored Petri nets is a Petri net modeling concept which extend quantitative and qualitative Petri nets by combining the capabilities of programing languages to describe data types and operations. It adds the concept of "color" to distinguish tokens and arc expressions that specify which token can flow over the arcs. Moreover, Boolean expressions (guards) can be defined in the transitions defining additional constrains to enable it. This appendix gives a formal description of the Colored Petri Net method as used in Chapters 2, 4 and 5.

Colored Petri nets: Formal definition

Following [73], we use Type ($Vars$) to denote the set of types $\{Type(v) | \ v \in Vars\}$ of a typed set Vars. To denote the Boolean type, we use the set B consisting of the elements {false, true}.

A *multi-set* m over a nonempty set S is a *function* $m : S \to \mathbb{N}$. An element $s \in S$ is said to belong to the multi-set m if $m(s) \neq 0$, and then we write $s \in m$. The integer $m(s)$ is the number of appearances of the element s in m.

We represent a multi-set m over S by the formal sum:

$$\sum_{s \in S} m(s)'s. \tag{C1}$$

By S_{MS} we denote the set of all multi-sets over S.

A colored qualitative Petri net is a tuple $(\Sigma, P, T, A, C, G, E, I)$, where

- Σ is a finite nonempty set of types, called color-sets;
- P is a finite nonempty set of places;
- T is a finite nonempty set of transitions
- A is a finite set of arcs
- C is a color function, it is defined from P to Σ;
- G is a guard function, it is defined from T to Boolean expressions such that
$$\forall\, t \in T: \left[Type\big(G(t)\big) = B \wedge Type\left(Var\big(G(t)\big)\right) \subseteq \Sigma\right]. \tag{C2}$$
- E is an arc expression function, it is defined from A to expressions such that
$$\forall\, a \in A: \left[Type\big(E(a)\big) = C\big(p(a)\big) \wedge Type\left(Var\big(E(a)\big)\right) \subseteq \Sigma\right], \tag{C3}$$
where $p(a)$ is the place component of a;
- I is an initialization function (the initial marking), it is defined from P to multi-sets of colors such that
$$\forall\, p \in P: \left[Type\big(I(p)\big) \subseteq C(p)\right]. \tag{C4}$$

In general, a marking associates with each place P a multi-set over $C(p)$, that is, a marking assignes to each place a multi-set of "colored tokens".

In the formal definition of Colored Stochastic Petri nets, we replace the set of transitions T by T_U defined in (B1), and add the function V as defined in (B4). Therefore the formal definition of our SPN^C is denoted as:

$$SPN \cup QPN^C = (\Sigma, P, T_U, A, \mathrm{V}, C, G, E, I). \quad \text{(C5)}$$