

Asymptotical stability of continuous-time probabilistic logic networks based on transition rate

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Received 29 September 2021/Revised 24 December 2021/Accepted 5 February 2022/Published online 30 January 2023

Abstract The evolution of the probability distribution for a continuous-time probabilistic logic network (CT-PLN) is determined by its transition rate matrix (TRM), which is a constant matrix that can be identified from the observed data. In the literature, the asymptotical stability criterion of a CT-PLN is expressed by using the transition probability matrix of discretization under a specific sampling period. In this paper, we derive several improved criteria that are directly expressed in terms of the TRM. We prove that a CT-PLN is asymptotically stable with respect to a given set if and only if the largest invariant subset (LIS) in the set is non-empty and the complementary set of the LIS contains no invariant subset. Thus, the asymptotical stability of a CT-PLN can be verified by applying the existing LIS algorithm twice. In addition, the condition that the complementary set of the LIS contains no invariant subset can be replaced by one of the more easily verifiable conditions, namely, the reachability condition and the rank condition. The reachability condition states that the LIS is reachable from every state outside, and the rank condition states that the complementary sub-matrix of the TRM with respect to the LIS is of full rank. For a CT-PLN being not asymptotically stable, a method of determining the domain of attraction is proposed. Finally, examples are provided to demonstrate the advantages of the proposed method.

Keywords asymptotical stability, continuous-time probabilistic logic network, semi-tensor product of matrices, set stability

Citation Li Z T, Guo Y Q, Gui W H. Asymptotical stability of continuous-time probabilistic logic networks based on transition rate. *Sci China Inf Sci*, 2023, 66(3): 132201, <https://doi.org/10.1007/s11432-021-3430-7>

1 Introduction

Developing a complete control theory for complex biological systems has always been a significant subject in the field of systems biology [1]. One fundamental step towards achieving this goal involves the selection of a suitable mathematical model that describes the essential dynamical behavior of biological systems and is convenient for synthesis. Logic dynamical networks (LDNs), such as discrete-time Boolean networks [2] and discrete-time probabilistic Boolean networks [3], are extensively-employed mathematical models for gene regulatory networks (GRNs). To better characterize the continuous-time evolution behaviors, continuous-time Boolean networks [4, 5] and continuous-time probabilistic Boolean networks [6] have been adopted to simulate GRNs. However, establishing a unified method for the analysis and control design of LDNs is difficult. The semi-tensor product (STP) of matrices and the theory of the vector representation of logic [7] have established a unified theoretical framework for LDNs. Over the past few years, many control-related problems for LDNs have been studied within this new framework [7–22].

Stability is the most basic requirement for any practical system. Guo et al. [23] investigated asymptotical stability and asymptotical feedback stabilization for continuous-time probabilistic logic networks (CT-PLNs), in which the stability criterion was expressed in terms of the transition probability matrix (TPM). For a CT-PLN, the TPM is a matrix-valued function of time generated by the transition rate matrix (TRM) using the matrix exponential. The TRM is a constant matrix that can be identified from the experimental data [6]. Thus, it is more convenient to express the stability criteria in terms of the TRM. This is the basic motivation for this study. Nevertheless, the TRM does not directly represent the

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Table 1 Notations

Notation	Definition	Notation	Definition
\mathbf{A}^T	Transpose of matrix \mathbf{A}	$\mathcal{S} \setminus \mathcal{T}$	Set $\{x \in \mathcal{S} x \notin \mathcal{T}\}$
$\mathbf{1}_n$	n -dimensional vector $(1, 1, \dots, 1)^T$	\mathcal{S}^c ($\mathcal{S} \subseteq \Delta_n$)	Set $\Delta_n \setminus \mathcal{S}$
$\mathbf{0}_n$	n -dimensional vector $(0, 0, \dots, 0)^T$	δ_n^{i-}	Set $\Delta_n \setminus \{\delta_n^i\}$
$\text{Row}_i(\mathbf{A})$	The i -th row of matrix \mathbf{A}	$[a : b]$	Set of integers k with $a \leq k \leq b$
$\text{Col}_j(\mathbf{A})$	The j -th column of matrix \mathbf{A}	Idx	Mapping $\text{Idx} : \delta_n^i \mapsto i$ with $i \in [1 : n]$
\mathbf{I}_n	n -order identity matrix	$\text{Idx}(\mathcal{M})$	Set $\{\text{Idx}(x) x \in \mathcal{M}\}$
δ_n^j	$\text{Col}_j(\mathbf{I}_n)$	$[\beta]_i$	The i -th component of vector β
Δ_n	Set $\{\delta_n^1, \delta_n^2, \dots, \delta_n^n\}$	$[\mathbf{A}]_{i,j}$	The (i, j) -th entry of matrix \mathbf{A}
$ \mathcal{S} $	Cardinality of set \mathcal{S}	$\mathbf{A} \succ \mathbf{0}$	$[\mathbf{A}]_{i,j} > 0, \forall i, j$

transition probability between states. To establish the TRM-based stability criteria, we must directly relate the reachability between states to the transition rates of probability, which is a non-trivial task.

In this study, we establish several TRM-based stability criteria for CT-PLNs, which are easier to verify than the existing TPM-based criteria. First, based on the invariant subset theory developed for CT-PLNs, we prove that a CT-PLN is asymptotically stable with respect to a given set if and only if the following conditions (a) and (b) are satisfied.

- (a) The largest invariant subset (LIS) contained in the given set is non-empty.
- (b) The complementary set of the LIS contains no non-empty invariant subset.

The LIS in any set can be directly calculated from the TRM by using an LIS algorithm, and the asymptotical stability of a CT-PLN can be verified by calling the algorithm twice.

Second, we prove that condition (b) can be replaced by more convenient conditions. The first alternative condition is called the reachability condition:

- (b') The LIS is reachable from every state outside with a positive probability.

Condition (b') is equivalent to the condition that, in the state transition rate graph (STRG), every state outside the LIS has a path to the inside. We propose a new reachability matrix to characterize the existence of a path between any two states. Unlike the definition in [23], the reachability matrix in this study is defined in terms of the TRM instead of the TPM, using which condition (b') can be easily verified.

The second alternative condition for condition (b) is called the rank condition:

- (b'') The complementary sub-matrix of the TRM with respect to the LIS is of full rank.

The complementary sub-matrix of the TRM with respect to the LIS is the sub-matrix obtained by deleting the rows and columns corresponding to the states in the LIS. Based on conditions (b') and (b''), the asymptotical stability of a CT-PLN can be verified by calling the LIS algorithm only once. Particularly, the asymptotical stability with respect to a fixed point can be evaluated directly by using the reachability condition or the rank condition. Moreover, in the case that a CT-PLN is not asymptotically stable with respect to the given set, a method to determine the domain of attraction is proposed.

The remainder of this paper is organized as follows. The notations throughout this paper are listed in Table 1. The model description of CT-PLNs is presented in Section 2. The main results are presented in Section 3. Examples are presented in Section 4, and the conclusion is drawn in Section 5.

2 Model description of CT-PLNs

Consider a CT-PLN with n nodes. The state of the i -th node at time t is defined as $X_i(t)$ which belongs to the r_i -valued logic domain, $\mathcal{D}_{r_i} := [0 : r_i - 1]$, with $r_i \in \{2, 3, \dots\}, \forall i \in [1 : n]$. Moreover, the state of the entire network at time t is defined as $X(t) = (X_1(t), X_2(t), \dots, X_n(t)) \in \mathcal{D}_{\mathbf{r}} := \mathcal{D}_{r_1} \times \mathcal{D}_{r_2} \times \dots \times \mathcal{D}_{r_n}$, with $\mathbf{r} := (r_1, r_2, \dots, r_n)$. For each $i \in [1 : n]$, let $x_i(t) := \delta_{r_i}^{r_i - X_i(t)}$ denote the vector form of $X_i(t)$. In addition, let $x(t) := x_1(t) \times x_2(t) \times \dots \times x_n(t) \in \Delta_N$ denote the vector form of $X(t)$, where $N := r_1 r_2 \dots r_n$ and “ \times ” denotes the STP of matrices [7].

In this study, the CT-PLN is modeled as a continuous-time homogeneous Markov chain with a state space Δ_N . Then, the transition probability between any two states is only related to the time interval θ . Let $\mathbf{P}(\theta)$ denote the TPM of the network, with

$$[\mathbf{P}(\theta)]_{i,j} = \Pr \{x(t + \theta) = \delta_N^j | x(t) = \delta_N^i\} \quad (1)$$

for any time t , which satisfies $\lim_{\theta \rightarrow 0^+} \mathbf{P}(\theta) = \mathbf{P}(0) = I_N$ and $\mathbf{P}(\alpha + \beta) = \mathbf{P}(\alpha)\mathbf{P}(\beta), \forall \alpha, \beta \geq 0$. The right derivative of $\mathbf{P}(\theta)$ at $\theta = 0$ exists and is finite [24]. The TRM is defined as

$$\mathbf{Q} := \lim_{\Delta\theta \rightarrow 0^+} \frac{\mathbf{P}(\Delta\theta) - \mathbf{P}(0)}{\Delta\theta}, \tag{2}$$

which satisfies

- (i) $[\mathbf{Q}]_{i,i} \leq 0, \forall i \in [1 : N]$;
- (ii) $[\mathbf{Q}]_{i,j} \geq 0, \forall i, j \in [1 : N]$ with $i \neq j$; and
- (iii) $\sum_{i=1}^N [\mathbf{Q}]_{i,j} = 0, \forall j \in [1 : N]$.

The matrices $\mathbf{P}(\theta)$ and \mathbf{Q} are related via the Kolmogorov equation $\dot{\mathbf{P}}(\theta) = \mathbf{Q}\mathbf{P}(\theta)$. Thus, $\mathbf{P}(\theta) = e^{\mathbf{Q}\theta}$. We use $\mathbf{Q}[\mathbf{r}]$ to represent a CT-PLN with TRM \mathbf{Q} and quantification level vector \mathbf{r} , and we use $x(t; x_0)$ to represent the solution to the CT-PLN, $\mathbf{Q}[\mathbf{r}]$, with initial state $x(0) = x_0$.

The STRG of the CT-PLN, $\mathbf{Q}[\mathbf{r}]$, is a weighted digraph, $\mathcal{D} = (\mathcal{V}, \mathcal{E}, w)$, where $\mathcal{V} := \Delta_N$ denotes the vertex set; $\mathcal{E} := \{(\delta_N^j, \delta_N^i) \in \Delta_N \times \Delta_N | [\mathbf{Q}]_{i,j} > 0\}$ represents the directed edge set, and $e = (\delta_N^j, \delta_N^i) \in \mathcal{E}$ is called the directed edge from δ_N^j to δ_N^i ; $w : \mathcal{E} \rightarrow (0, +\infty)$ is the weight of the directed edge, and $w(e) := [\mathbf{Q}]_{i,j}$ for every $e = (\delta_N^j, \delta_N^i) \in \mathcal{E}$. The weighted matrix \mathbf{W} of the STRG is an N -order matrix with $[\mathbf{W}]_{i,j} := w(e)$ for $e = (\delta_N^j, \delta_N^i) \in \mathcal{E}$, and $[\mathbf{W}]_{i,j} := 0$ otherwise. In fact, it is valid that $[\mathbf{W}]_{i,j} = [\mathbf{Q}]_{i,j}$ for $i \neq j$ and $[\mathbf{W}]_{i,j} = 0$ for $i = j$. The reachability matrix \mathbf{R} is defined as

$$\mathbf{R} := I_N + \sum_{v=1}^{N-1} \mathbf{W}^v. \tag{3}$$

Lemma 1 (Lévy dichotomy [25]). Assume that \mathbf{Q} is the TRM of the CT-PLN $\mathbf{Q}[\mathbf{r}]$. Then, for any $i, j \in [1 : N]$ with $i \neq j$, there exists a $\bar{t} > 0$, such that $[e^{\mathbf{Q}t}]_{i,j} > 0$ if and only if $[e^{\mathbf{Q}\bar{t}}]_{i,j} > 0$ holds for any $t > 0$.

Lemma 2 ([26]). Assume that \mathbf{Q} is the TRM of the CT-PLN $\mathbf{Q}[\mathbf{r}]$. Then, for any $i, j \in [1 : N]$ with $i \neq j$, $[e^{\mathbf{Q}t}]_{i,j} > 0$ for any $t > 0$ if and only if the STRG has a path from δ_N^j to δ_N^i .

Remark 1. It was proved in [26] that for a continuous-time homogeneous Markov chain with a countable infinity of states, the transition probability from state j to state i with $i \neq j$ is positive if and only if there is a finite positive transition rate chain from state j to state i . It is easily checked that this conclusion is also valid for a continuous-time finite homogeneous Markov chain. Based on this, we give Lemma 2 without proof.

Lemma 3. Assume that \mathbf{Q} is the TRM of the CT-PLN $\mathbf{Q}[\mathbf{r}]$. Then, for any $i, j \in [1 : N]$ with $i \neq j$, $[e^{\mathbf{Q}t}]_{i,j} > 0, \forall t > 0$ if and only if $[\mathbf{R}]_{i,j} > 0$.

Proof. (Necessity) According to Lemma 2, $[e^{\mathbf{Q}t}]_{i,j} > 0, \forall t > 0$ implies that the STRG has a path from δ_N^j to δ_N^i . Because the state space Δ_N is finite, we can find a simple path, i.e., a path without a loop, with the length being less than or equal to $N - 1$, from δ_N^j to δ_N^i . This means that either $[\mathbf{Q}]_{i,j} > 0$ or $[\mathbf{Q}]_{i,d_\ell} [\mathbf{Q}]_{d_\ell, d_{\ell-1}} \cdots [\mathbf{Q}]_{d_1, j} > 0$, where indices $j, d_1, d_2, \dots, d_\ell, i$ are pairwise distinct, and $\ell \leq N - 2$. Thus,

$$\begin{aligned} [\mathbf{R}]_{i,j} &= \left[I_N + \sum_{v=1}^{N-1} \mathbf{W}^v \right]_{i,j} \\ &\geq [\mathbf{W}^{\ell+1}]_{i,j} \\ &\geq [\mathbf{W}]_{i,d_\ell} [\mathbf{W}]_{d_\ell, d_{\ell-1}} \cdots [\mathbf{W}]_{d_1, j} \\ &= [\mathbf{Q}]_{i,d_\ell} [\mathbf{Q}]_{d_\ell, d_{\ell-1}} \cdots [\mathbf{Q}]_{d_1, j} > 0. \end{aligned} \tag{4}$$

(Sufficiency) According to (3), $[\mathbf{R}]_{i,j} > 0$ implies that there exists an $\ell \in [1 : N - 1]$, such that $[\mathbf{W}^\ell]_{i,j} > 0$; i.e., there exists a path from δ_N^j to δ_N^i in the STRG. This yields $[e^{\mathbf{Q}t}]_{i,j} > 0, \forall t > 0$ according to Lemma 2.

Remark 2. Since for any $i \in [1 : N]$, $[e^{\mathbf{Q}t}]_{i,i} > 0, \forall t \geq 0$ is valid¹⁾ and $[\mathbf{R}]_{i,i} > 0$ according to (3), we ignore the discussion for the case of $i = j$ in Lemma 3.

1) This claim can be deduced from the result of page 143 in [24].

3 Asymptotical stability of CT-PLNs

3.1 Definition of stability and invariant subset

Definition 1. Consider a CT-PLN $\mathbf{Q}[\mathbf{r}]$.

(1) The domain of attraction of a given set $\mathcal{M} \subseteq \Delta_N$ is defined as

$$\mathcal{A}(\mathcal{M}) := \left\{ x_0 \in \Delta_N \mid \lim_{t \rightarrow +\infty} \Pr\{x(t; x_0) \in \mathcal{M}\} = 1 \right\}. \tag{5}$$

(2) The network is said to be asymptotically stable with respect to $x_e \in \Delta_N$, if $\mathcal{A}(\{x_e\}) = \Delta_N$. The network is said to be asymptotically stable with respect to $\mathcal{M} \subseteq \Delta_N$, if $\mathcal{A}(\mathcal{M}) = \Delta_N$ (see [23]).

Remark 3. The case of $\mathcal{M} = \Delta_N$ is trivial because any CT-PLN $\mathbf{Q}[\mathbf{r}]$ is asymptotically stable with respect to its state space Δ_N . Therefore, we always assume $\mathcal{M} \neq \Delta_N$ in this study.

Definition 2 ([23]). A subset, $\mathcal{I} \subseteq \Delta_N$, is said to be an invariant subset of CT-PLN $\mathbf{Q}[\mathbf{r}]$, if for any initial state, $x_0 \in \mathcal{I}$, $\Pr\{x(t; x_0) \in \mathcal{I}\} = 1$ holds for any $t \geq 0$. The union of all invariant subsets contained in subset $\mathcal{M} \subseteq \Delta_N$ is also invariant, and it is defined as $\mathcal{I}(\mathcal{M})$, which is called the LIS of CT-PLN $\mathbf{Q}[\mathbf{r}]$ with respect to \mathcal{M} .

Proposition 1 ([23]). A subset, $\mathcal{I} \subseteq \Delta_N$, is an invariant subset of CT-PLN $\mathbf{Q}[\mathbf{r}]$ if and only if

$$\sum_{i \in \text{Idx}(\mathcal{I})} [\mathbf{Q}]_{i,j} = 0, \quad \forall j \in \text{Idx}(\mathcal{I}). \tag{6}$$

For a given sampling period T , the sampling sequence $\xi_T(k) := x(kT), k \in \{0, 1, 2, \dots\}$ of the CT-PLN $\mathbf{Q}[\mathbf{r}]$ is a discrete-time homogeneous Markov chain with its 1-step TPM, $\mathbf{P} = e^{\mathbf{Q}T}$. In this study, the LIS of $\xi_T(k)$ in $\mathcal{M} \subseteq \Delta_N$ is defined as $\mathcal{I}_T(\mathcal{M})$. Please refer to [12] for the definition of the LIS for discrete-time homogeneous Markov chains.

Lemma 4. A subset, $\mathcal{I} \subseteq \Delta_N$, is an invariant subset of CT-PLN $\mathbf{Q}[\mathbf{r}]$ if and only if it is also an invariant subset of $\xi_T(k)$ under any given sampling period T .

Proof. This claim can be deduced from the proof of Proposition 1. Please refer to [23].

3.2 TRM-based criteria for asymptotical stability

Theorem 1. CT-PLN $\mathbf{Q}[\mathbf{r}]$ is asymptotically stable with respect to $\mathcal{M} \subseteq \Delta_N$ if and only if $\mathcal{I}(\mathcal{M}) \neq \emptyset$ and $\mathcal{I}([\mathcal{I}(\mathcal{M})]^c) = \emptyset$.

Proof. (Necessity) If CT-PLN $\mathbf{Q}[\mathbf{r}]$ is asymptotically stable with respect to \mathcal{M} , then for any positive number T , $\xi_T(k)$ is stable in distribution²⁾ with respect to \mathcal{M} . According to Theorem 3 in [12] and Lemma 4, $\mathcal{I}(\mathcal{M}) = \mathcal{I}_T(\mathcal{M}) \neq \emptyset$ and $\mathcal{I}([\mathcal{I}(\mathcal{M})]^c) = \mathcal{I}_T([\mathcal{I}_T(\mathcal{M})]^c) = \emptyset$.

(Sufficiency) If $\mathcal{I}(\mathcal{M}) \neq \emptyset$ and $\mathcal{I}([\mathcal{I}(\mathcal{M})]^c) = \emptyset$, then according to Lemma 4, for any $\bar{T} > 0$, $\mathcal{I}_{\bar{T}}(\mathcal{M}) = \mathcal{I}(\mathcal{M}) \neq \emptyset$ and $\mathcal{I}_{\bar{T}}([\mathcal{I}_{\bar{T}}(\mathcal{M})]^c) = \mathcal{I}([\mathcal{I}(\mathcal{M})]^c) = \emptyset$. This implies that $\xi_{\bar{T}}(k)$ has no invariant subsets in $[\mathcal{I}_{\bar{T}}(\mathcal{M})]^c$. Thus, for every $x_0 \in [\mathcal{I}_{\bar{T}}(\mathcal{M})]^c$, there exists a positive integer $k_{x_0} \in [1 : N - |\mathcal{I}_{\bar{T}}(\mathcal{M})|]$, such that $\Pr\{x(k_{x_0}\bar{T}; x_0) \in \mathcal{I}_{\bar{T}}(\mathcal{M})\} > 0$. According to the non-decreasing property of the transition probability from any state to an invariant subset [12], it is valid that

$$\Pr\{x(\bar{k}\bar{T}; x_0) \in \mathcal{I}_{\bar{T}}(\mathcal{M})\} > 0, \quad \forall x_0 \in [\mathcal{I}_{\bar{T}}(\mathcal{M})]^c, \tag{7}$$

where $\bar{k} := \max_{x_0 \in [\mathcal{I}_{\bar{T}}(\mathcal{M})]^c} k_{x_0}$. Thus, for any $x_0 \in \Delta_N$, $\Pr\{x(\bar{k}\bar{T}; x_0) \in \mathcal{I}_{\bar{T}}(\mathcal{M})\} > 0$ is valid. According to Theorem 3 and Proposition 2 in [12], it is valid that

$$\lim_{n \rightarrow \infty} \sum_{v \in \text{Idx}(\mathcal{I}_{\bar{T}}(\mathcal{M}))} \text{Row}_v((e^{\mathbf{Q}\bar{T}})^n) = \mathbf{1}_N^T. \tag{8}$$

According to Proposition 2 in [23] and Lemma 4, it is valid that

$$\lim_{t \rightarrow +\infty} \sum_{v \in \text{Idx}(\mathcal{I}(\mathcal{M}))} \text{Row}_v(e^{\mathbf{Q}t}) = \mathbf{1}_N^T. \tag{9}$$

Thus, CT-PLN $\mathbf{Q}[\mathbf{r}]$ is asymptotically stable with respect to \mathcal{M} owing to $\mathcal{I}(\mathcal{M}) \subseteq \mathcal{M}$.

2) Please refer to [12] for the definition of the stability in distribution for discrete-time homogeneous Markov chains.

Corollary 1. CT-PLN $\mathbf{Q}[r]$ is asymptotically stable with respect to $\delta_N^i \in \Delta_N$ if and only if $[\mathbf{Q}]_{i,i} = 0$ and $\mathcal{I}(\delta_N^i) = \emptyset$.

Remark 4. The proof of Theorem 1 shows that CT-PLN $\mathbf{Q}[r]$ is asymptotically stable with respect to $\mathcal{M} \subseteq \Delta_N$ if and only if it is asymptotically stable with respect to $\mathcal{I}(\mathcal{M})$.

The LIS in a given set can be calculated by using the LIS algorithm proposed in [23]. In the following, we show that condition $\mathcal{I}([\mathcal{I}(\mathcal{M})]^c) = \emptyset$ in Theorem 1 can be replaced by more convenient conditions. Thus, the asymptotical stability of a CT-PLN can be verified by calling the LIS algorithm only once. The first alternative condition is the reachability condition.

Theorem 2. CT-PLN $\mathbf{Q}[r]$ is asymptotically stable with respect to $\mathcal{M} \subseteq \Delta_N$ if and only if

- (1) $\mathcal{I}(\mathcal{M}) \neq \emptyset$ and
- (2) for any $\delta_N^v \in [\mathcal{I}(\mathcal{M})]^c$, the STRG has a path from δ_N^v to $\mathcal{I}(\mathcal{M})$; or equivalently,

$$\sum_{v \in \text{Idx}(\mathcal{I}(\mathcal{M}))} \text{Row}_v(\mathbf{R}) \succ 0. \tag{10}$$

Proof. According to Lemma 3, $\sum_{v \in \text{Idx}(\mathcal{I}(\mathcal{M}))} \text{Row}_v(\mathbf{R}) \succ 0$ if and only if for any $j \in \text{Idx}([\mathcal{I}(\mathcal{M})]^c)$, there exists an $i \in \text{Idx}(\mathcal{I}(\mathcal{M}))$, such that $[e^{\mathbf{Q}^t}]_{i,j} > 0, \forall t > 0$, i.e., $\mathcal{I}_T([\mathcal{I}_T(\mathcal{M})]^c) = \emptyset, \forall T > 0$, which is equivalent to $\mathcal{I}([\mathcal{I}(\mathcal{M})]^c) = \emptyset$ based on Lemma 4. Then according to Theorem 1, this claim holds.

Corollary 2. CT-PLN $\mathbf{Q}[r]$ is asymptotically stable with respect to $\delta_N^i \in \Delta_N$ if and only if

- (1) $[\mathbf{Q}]_{i,i} = 0$ and
- (2) for any $v \neq i$, the STRG has a path from δ_N^v to δ_N^i ; or equivalently, $\text{Row}_i(\mathbf{R}) \succ 0$.

In the following, we prove that condition $\mathcal{I}([\mathcal{I}(\mathcal{M})]^c) = \emptyset$ in Theorem 1 can be replaced by the rank condition.

Definition 3. Consider a CT-PLN $\mathbf{Q}[r]$. For a given non-empty subset $\mathcal{M} \subseteq \Delta_N$, the sub-matrix of \mathbf{Q} with respect to \mathcal{M} , which is defined as $\mathbf{Q}_{\mathcal{M}}$, is the sub-matrix of \mathbf{Q} obtained by deleting all rows and columns with indices within $\text{Idx}(\mathcal{M}^c)$. The sub-matrix of \mathbf{Q} with respect to \mathcal{M}^c is called the complementary sub-matrix of \mathbf{Q} with respect to \mathcal{M} .

Proposition 2. Consider a CT-PLN $\mathbf{Q}[r]$. Then, for a given non-empty subset $\mathcal{M} \subseteq \Delta_N$, $\mathcal{I}(\mathcal{M}) = \emptyset$ if and only if sub-matrix $\mathbf{Q}_{\mathcal{M}}$ is of full rank.

Proof. (Sufficiency) We prove the inverse negative proposition. If $\mathcal{I}(\mathcal{M}) \neq \emptyset$, then, according to Proposition 1 and the properties of the TRM, we can easily verify that $\mathbf{Q}_{\mathcal{I}(\mathcal{M})}$ is a TRM and $\det(\mathbf{Q}_{\mathcal{I}(\mathcal{M})}) = 0$. We define $r := |\mathcal{M}|$; then there exist an N -order permutation matrix \mathbf{M} and an r -order permutation matrix \mathbf{V} , such that

$$\mathbf{M}\mathbf{Q}\mathbf{M}^T = \begin{pmatrix} \mathbf{Q}_{\mathcal{M}} & * \\ * & * \end{pmatrix}, \quad \mathbf{V}\mathbf{Q}_{\mathcal{M}}\mathbf{V}^T = \begin{pmatrix} \mathbf{Q}_{\mathcal{I}(\mathcal{M})} & * \\ \mathbf{O} & * \end{pmatrix},$$

where \mathbf{O} denotes the zero matrix with the appropriate dimensions and “*” denotes a matrix block with the appropriate dimensions. Thus, $\mathbf{Q}_{\mathcal{M}}$ is singular.

(Necessity) If $\mathcal{I}(\mathcal{M}) = \emptyset$, then for every $j \in \text{Idx}(\mathcal{M})$,

$$\sum_{v \in \text{Idx}(\mathcal{M}^c)} [e^{\mathbf{Q}^t}]_{v,j} > 0, \quad \forall t > 0 \tag{11}$$

holds by using Lemma 1. Thus, for any $j \in \text{Idx}(\mathcal{M})$, the STRG has a path from δ_N^j to \mathcal{M}^c according to Lemma 2. We define

$$\bar{\mathbf{Q}} := \begin{pmatrix} \mathbf{Q}_{\mathcal{M}} & \mathbf{0}_r \\ \boldsymbol{\beta}^T & 0 \end{pmatrix}, \tag{12}$$

where $\boldsymbol{\beta}$ is an r -dimensional constant vector that is selected such that the sum of every column of $\bar{\mathbf{Q}}$ is zero. Thus, $\bar{\mathbf{Q}}$ can be regarded as the TRM of a CT-PLN with a state space Δ_{r+1} and a fixed point δ_{r+1}^{r+1} . Under these conditions, for any $j \in [1 : r]$, the STRG defined by $\bar{\mathbf{Q}}$ has a path from δ_{r+1}^j to δ_{r+1}^{r+1} . Note that

$$e^{\bar{\mathbf{Q}}} = I_{r+1} + \sum_{v=1}^{\infty} \frac{\bar{\mathbf{Q}}^v}{v!} = \begin{pmatrix} e^{\mathbf{Q}_{\mathcal{M}}} & \mathbf{0}_r \\ \boldsymbol{\gamma}^T & 1 \end{pmatrix}, \tag{13}$$

where

$$\gamma^T = \beta^T \left(I_r + \sum_{v=1}^{\infty} \frac{\mathbf{Q}_{\mathcal{M}}^v}{(v+1)!} \right). \tag{14}$$

Then according to Lemma 2, $\gamma \succ 0$. Consequently, $\rho(\mathbf{e}^{\mathbf{Q}_{\mathcal{M}}}) \leq \|\mathbf{e}^{\mathbf{Q}_{\mathcal{M}}}\|_1 < 1$, where $\rho(\cdot)$ and $\|\cdot\|_1$ denote the spectral radius and the one-norm of a square matrix, respectively; that is, $\mathbf{e}^{\mathbf{Q}_{\mathcal{M}}}$ is strictly Schur stable. Thus, $\mathbf{Q}_{\mathcal{M}}$ is of full rank.

Theorem 3. CT-PLN $\mathbf{Q}[\mathbf{r}]$ is asymptotically stable with respect to $\mathcal{M} \subseteq \Delta_N$ if and only if $\mathcal{I}(\mathcal{M}) \neq \emptyset$ and the complementary sub-matrix of \mathbf{Q} with respect to $\mathcal{I}(\mathcal{M})$ is of full rank.

Proof. This claim is a direct consequence of Theorem 1 and Proposition 2.

Corollary 3. CT-PLN $\mathbf{Q}[\mathbf{r}]$ is asymptotically stable with respect to $\delta_N^i \in \Delta_N$ if and only if

- (1) $[\mathbf{Q}]_{i,i} = 0$ and
- (2) $\text{rank}(\mathbf{Q}_{\delta_N^{i-}}) = N - 1$; or equivalently, $\det(\mathbf{Q}_{\delta_N^{i-}}) \neq 0$.

Corollary 4. CT-PLN $\mathbf{Q}[\mathbf{r}]$ is asymptotically stable with respect to $\delta_N^i \in \Delta_N$ if and only if $[\mathbf{Q}]_{i,i} = 0$ and $\text{rank}(\mathbf{Q}) = N - 1$.

Proof. Note that $[\mathbf{Q}]_{i,i} = 0$ implies that $\text{Col}_i(\mathbf{Q}) = \mathbf{0}_N$. Therefore, there exists an N -order permutation matrix \mathbf{M} , such that

$$\mathbf{M}\mathbf{Q}\mathbf{M}^T = \begin{pmatrix} 0 & \boldsymbol{\alpha}^T \\ \mathbf{0}_{N-1} & \mathbf{Q}_{\delta_N^{i-}} \end{pmatrix}, \tag{15}$$

where $\boldsymbol{\alpha}^T = ([\mathbf{Q}]_{i,1}, [\mathbf{Q}]_{i,2}, \dots, [\mathbf{Q}]_{i,i-1}, [\mathbf{Q}]_{i,i+1}, \dots, [\mathbf{Q}]_{i,N})$. This implies that

$$\begin{aligned} \text{rank}(\mathbf{Q}) &= \text{rank}(\mathbf{M}\mathbf{Q}\mathbf{M}^T) \\ &= \text{rank} \begin{pmatrix} 0 & \mathbf{0}_{N-1}^T \\ \mathbf{0}_{N-1} & \mathbf{Q}_{\delta_N^{i-}} \end{pmatrix} = \text{rank}(\mathbf{Q}_{\delta_N^{i-}}), \end{aligned} \tag{16}$$

where the second equality is derived by adding $\text{Row}_v(\mathbf{M}\mathbf{Q}\mathbf{M}^T)$ to $\text{Row}_1(\mathbf{M}\mathbf{Q}\mathbf{M}^T)$ for every $v \in [2 : N]$ and combining it with the properties of the TRM. Thus, according to Corollary 3, the claim holds.

Remark 5. Compared with the TPM-based results presented in [23], the main advantage of the TRM-based stability criteria proposed in this study is that the TRM is a constant matrix, which contains the complete information needed to determine the stability. Thus, we avoid the unnecessary calculation of the TPM of the discretized CT-PLN under a specific sampling period.

3.3 Domain of attraction for non-asymptotically stable CT-PLNs

Theorem 4. Assume that CT-PLN $\mathbf{Q}[\mathbf{r}]$ is not asymptotically stable with respect to a given non-empty subset $\mathcal{M} \subseteq \Delta_N$. Then $\mathcal{A}(\mathcal{M}) = \Theta$ with

$$\Theta := \left\{ \delta_N^j \in \Delta_N \mid \sum_{v \in \text{Idx}(\mathcal{I}([\mathcal{I}(\mathcal{M})]^c))} [\mathbf{R}]_{v,j} = 0 \right\}. \tag{17}$$

Proof. According to Theorem 1, CT-PLN $\mathbf{Q}[\mathbf{r}]$ being not asymptotically stable with respect to \mathcal{M} implies that either $\mathcal{I}(\mathcal{M}) = \emptyset$ or $\mathcal{I}([\mathcal{I}(\mathcal{M})]^c) \neq \emptyset$. If $\mathcal{I}(\mathcal{M}) = \emptyset$, then, $\mathcal{A}(\mathcal{M}) = \emptyset$. In this case, Eq. (17) is verified. In the following, we assume that $\mathcal{I}(\mathcal{M}) \neq \emptyset$ and $\mathcal{I}([\mathcal{I}(\mathcal{M})]^c) \neq \emptyset$.

First, we prove $\Theta \subseteq \mathcal{A}(\mathcal{M})$. Indeed, according to the definition of $\mathcal{I}([\mathcal{I}(\mathcal{M})]^c)$ and (17), it is valid that $\mathcal{I}(\Theta) = \Theta$, and for any $\delta_N^j \in \Theta \setminus \mathcal{I}(\mathcal{M})$, the STRG of CT-PLN $\mathbf{Q}[\mathbf{r}]$ has a path from δ_N^j to $\mathcal{I}(\mathcal{M})$. Then, the sub-matrix \mathbf{Q}_{Θ} is a TRM. We define $b := |\Theta|$ and construct a bijection $\eta : \Theta \rightarrow \Delta_b$ with $\eta(\delta_N^{i_h}) = \delta_b^h, h \in [1 : b]$. Moreover, we define $\eta(\mathcal{G}) := \{\eta(g) | g \in \mathcal{G}\}$ for a non-empty subset $\mathcal{G} \subseteq \Theta$. Then, for any $\delta_N^j \in \Theta \setminus \mathcal{I}(\mathcal{M})$, the STRG of the CT-PLN with the TRM \mathbf{Q}_{Θ} and the state space Δ_b also has a path from $\eta(\delta_N^j)$ to $\eta(\mathcal{I}(\mathcal{M}))$. Let $\tilde{x}(t)$ denote the state vector of this network in the vector form. Then, according to Theorem 2, it is valid that

$$\lim_{t \rightarrow +\infty} \Pr \{ \tilde{x}(t; \eta(\delta_N^j)) \in \eta(\mathcal{I}(\mathcal{M})) \} = 1, \quad \forall \delta_N^j \in \Theta. \tag{18}$$

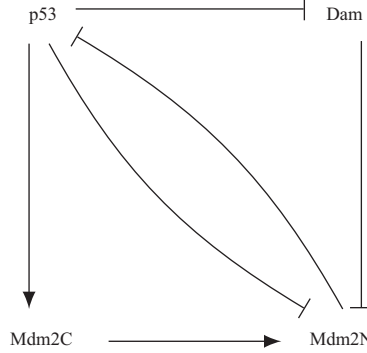


Figure 1 Four-node network for the p53-Mdm2 model. Normal and blunt arrows indicate positive and negative regulation, respectively.

Note that $\mathcal{I}(\mathcal{M}) \subseteq \mathcal{M}$ implies that $\eta(\mathcal{I}(\mathcal{M})) \subseteq \eta(\mathcal{M})$; then Eq. (18) yields

$$\lim_{t \rightarrow +\infty} \Pr \{ \tilde{x}(t; \eta(\delta_N^j)) \in \eta(\mathcal{M}) \} = 1, \quad \forall \delta_N^j \in \Theta, \quad (19)$$

namely,

$$\lim_{t \rightarrow +\infty} \Pr \{ x(t; \delta_N^j) \in \mathcal{M} \} = 1, \quad \forall \delta_N^j \in \Theta. \quad (20)$$

Thus, $\Theta \subseteq \mathcal{A}(\mathcal{M})$.

Second, we prove $\mathcal{A}(\mathcal{M}) \subseteq \Theta$ by showing that $\Theta^c \subseteq [\mathcal{A}(\mathcal{M})]^c$. Indeed, Eq. (17) implies that for any $\delta_N^j \in \Theta^c \setminus \mathcal{I}([\mathcal{I}(\mathcal{M})]^c)$, the STRG of CT-PLN $\mathbf{Q}[\mathbf{r}]$ has a path from δ_N^j to $\mathcal{I}([\mathcal{I}(\mathcal{M})]^c)$. According to Lemma 3, there exists a positive number T , such that

$$\sum_{v \in \text{Idx}(\mathcal{I}([\mathcal{I}(\mathcal{M})]^c))} [e^{\mathbf{Q}T}]_{v,j} = \varepsilon_j > 0. \quad (21)$$

By using Proposition 2 in [23], we obtain that

$$\sum_{v \in \text{Idx}(\mathcal{I}([\mathcal{I}(\mathcal{M})]^c))} [e^{\mathbf{Q}t}]_{v,j} \geq \varepsilon_j > 0, \quad \forall t \geq T, \quad (22)$$

$$\lim_{t \rightarrow +\infty} \sum_{v \in \text{Idx}(\mathcal{I}([\mathcal{I}(\mathcal{M})]^c))} [e^{\mathbf{Q}t}]_{v,j} \geq \varepsilon_j, \quad (23)$$

and $\lim_{t \rightarrow +\infty} \sum_{v \in \text{Idx}(\mathcal{I}(\mathcal{M}))} [e^{\mathbf{Q}t}]_{v,j}$ exists. This yields

$$\lim_{t \rightarrow +\infty} \sum_{v \in \text{Idx}(\mathcal{I}(\mathcal{M}))} [e^{\mathbf{Q}t}]_{v,j} \leq 1 - \lim_{t \rightarrow +\infty} \sum_{v \in \text{Idx}(\mathcal{I}([\mathcal{I}(\mathcal{M})]^c))} [e^{\mathbf{Q}t}]_{v,j} \leq 1 - \varepsilon_j < 1. \quad (24)$$

Namely, $\delta_N^j \notin \mathcal{A}(\mathcal{M})$. Moreover, note that $\delta_N^j \notin \mathcal{A}(\mathcal{M})$ is obviously valid for any $\delta_N^j \in \mathcal{I}([\mathcal{I}(\mathcal{M})]^c)$. Thus, $\Theta^c \subseteq [\mathcal{A}(\mathcal{M})]^c$.

4 Examples

Example 1. We consider the four-node network shown in Figure 1, which describes the mutual regulatory relationship between protein p53, cytoplasmic Mdm2 (Mdm2C), nuclear Mdm2 (Mdm2N), and DNA damage (Dam) in the process of p53 response DNA damage [27]. Specifically, Dam induced by external stress down-regulates the level of Mdm2N, Mdm2N down-regulates the level of protein p53, Mdm2C up-regulates Mdm2N, and protein p53 up-regulates the level of Mdm2C and down-regulates the levels of Mdm2N and Dam. Normally, p53 remains at a low level, since persistently high levels of p53 may cause cell death. DNA damage leads to an increase of the level of active p53, which can activate the damage repair process [27].

This network is modeled as a CT-PLN $\mathbf{Q}[\mathbf{r}]$, where $\mathbf{r} = (r_1, r_2, r_3, r_4) = (3, 2, 2, 2)$; r_1 , r_2 , r_3 , and r_4 represent the quantification levels of p53, Mdm2C, Mdm2N, and Dam, respectively. We use $X_1(t)$, $X_2(t)$,

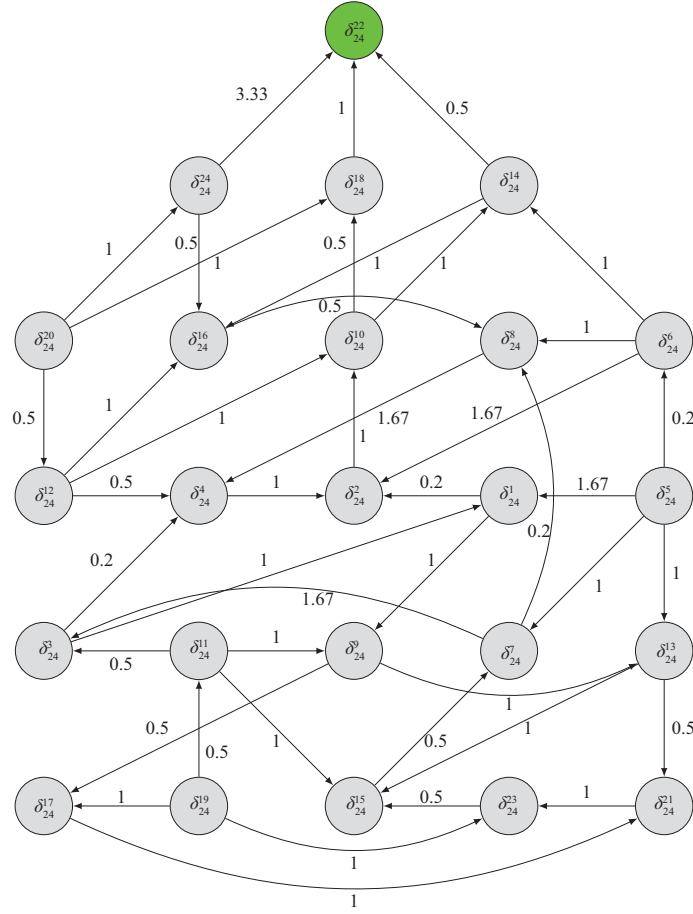


Figure 2 (Color online) The STRG of the p53-Mdm2 model. The state colored in green represents the equilibrium point.

$X_3(t)$, and $X_4(t)$ to represent the quantized values of p53, Mdm2C, Mdm2N, and Dam at time t , respectively, and use $x_1(t), x_2(t), x_3(t)$, and $x_4(t)$ to represent their corresponding vector forms. Then $x_1(t) \in \Delta_3$ and $x_i(t) \in \Delta_2, i \in [2 : 4]$. Let $X(t) := (X_1(t), X_2(t), X_3(t), X_4(t)) \in \mathcal{D}_3 \times \mathcal{D}_2 \times \mathcal{D}_2 \times \mathcal{D}_2$ denote the state of the entire network and $x(t) := x_1(t) \times x_2(t) \times x_3(t) \times x_4(t) \in \Delta_{24}$ denote the vector form of $X(t)$. The STRG of the network is plotted in Figure 2, where the transition rates labelled on the directed edges are obtained from [6]. Then, the TRM Q can be easily obtained from the STRG, which is omitted here. The STRG shows that $x_e = \delta_{24}^{22}$ is the only equilibrium point; thus, every state has a path to x_e . By Theorem 2, this information suffices to assert the asymptotical stability with respect to δ_{24}^{22} . This demonstrates the advantage of the TRM-based stability criteria over the TPM-based ones obtained in [23].

Example 2. We consider a three-node CT-PLN $Q[r]$ with $r = (r_1, r_2, r_3) = (2, 2, 2)$. Let $x(t) := x_1(t) \times x_2(t) \times x_3(t) \in \Delta_8$ denote the state vector in the vector form, and assume that the TRM of this CT-PLN is as follows:

$$Q = \begin{pmatrix} -1 & 0 & 2 & 0 & 0 & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 & 2 & 0 & 0 & 0 \\ 1 & 0 & -2 & 0 & 0 & 0 & 0 & 0.8 \\ 0 & 0 & 0 & -1.5 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0.5 & -2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -1 & 0.7 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -1.7 & 2.2 \\ 0 & 0 & 0 & 1.0 & 0 & 0 & 1.0 & -3.0 \end{pmatrix}. \tag{25}$$

We consider the asymptotical stability with respect to $\mathcal{M} = \{\delta_8^1, \delta_8^2, \delta_8^3, \delta_8^4, \delta_8^5\}$. Using the LIS algorithm

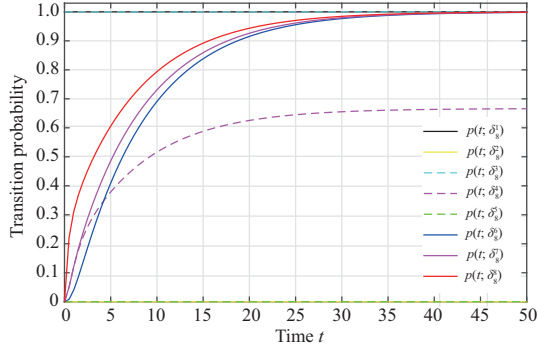


Figure 3 (Color online) The transition probability curves from different initial states to $\mathcal{I}(\mathcal{M})$.

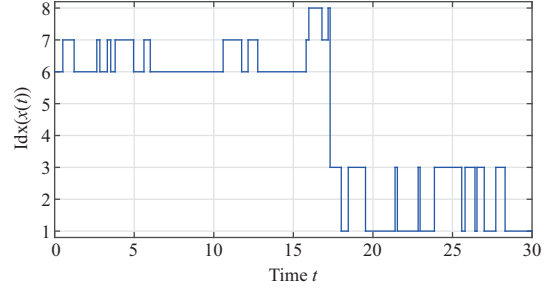


Figure 4 (Color online) A sampling state trajectory of the network with initial state δ_8^6 .

proposed in [23], we obtain $\mathcal{I}(\mathcal{M}) = \{\delta_8^1, \delta_8^2, \delta_8^3, \delta_8^5\}$ and $\mathcal{I}([\mathcal{I}(\mathcal{M})]^c) = \emptyset$. According to Theorem 1, this CT-PLN is asymptotically stable with respect to \mathcal{M} . We can also verify the reachability condition and the rank condition. First, the reachability matrix \mathbf{R} is calculated by using (3), thereby showing that $\text{Row}_1(\mathbf{R}) + \text{Row}_2(\mathbf{R}) + \text{Row}_3(\mathbf{R}) + \text{Row}_5(\mathbf{R}) \succ 0$. This verifies the reachability condition. Second, the complementary sub-matrix of \mathbf{Q} with respect to $\mathcal{I}(\mathcal{M})$ is

$$\mathbf{Q}_{[\mathcal{I}(\mathcal{M})]^c} = \begin{pmatrix} -1.5 & 0 & 0 & 0 \\ 0 & -1 & 0.7 & 0 \\ 0 & 1 & -1.7 & 2.2 \\ 1.0 & 0 & 1.0 & -3.0 \end{pmatrix}. \quad (26)$$

$\mathbf{Q}_{[\mathcal{I}(\mathcal{M})]^c}$ is easily determined as nonsingular. Thus, the rank condition is also verified.

Next, we consider the asymptotical stability with respect to $\tilde{\mathcal{M}} = \{\delta_8^1, \delta_8^2, \delta_8^3\}$. Using the LIS algorithm proposed in [23], we obtain $\mathcal{I}(\tilde{\mathcal{M}}) = \{\delta_8^1, \delta_8^3\}$ and $\mathcal{I}([\mathcal{I}(\tilde{\mathcal{M})}]^c) = \{\delta_8^2, \delta_8^5\}$. According to Theorem 1, this CT-PLN is not asymptotically stable with respect to $\tilde{\mathcal{M}}$. Moreover, it is easily verified that $[\text{Row}_1(\mathbf{R}) + \text{Row}_3(\mathbf{R})]_v = 0, \forall v \in \{2, 5\}$, and the complementary sub-matrix of \mathbf{Q} with respect to $\mathcal{I}(\tilde{\mathcal{M}})$ is

$$\mathbf{Q}_{[\mathcal{I}(\tilde{\mathcal{M}})]^c} = \begin{pmatrix} -1 & 0 & 2 & 0 & 0 & 0 \\ 0 & -1.5 & 0 & 0 & 0 & 0 \\ 1 & 0.5 & -2 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1 & 0.7 & 0 \\ 0 & 0 & 0 & 1 & -1.7 & 2.2 \\ 0 & 1.0 & 0 & 0 & 1.0 & -3.0 \end{pmatrix}. \quad (27)$$

$\mathbf{Q}_{[\mathcal{I}(\tilde{\mathcal{M}})]^c}$ is easily determined as singular. Thus, both the reachability condition and the rank condition are verified. In addition, according to Theorem 4, the domain of attraction of $\tilde{\mathcal{M}}$ is $\mathcal{A}(\tilde{\mathcal{M}}) = \{\delta_8^1, \delta_8^3, \delta_8^6, \delta_8^7, \delta_8^8\}$. The transition probability curves from every initial state to $\mathcal{I}(\tilde{\mathcal{M}})$ are plotted in Figure 3, where for every initial state $x_0 = \delta_8^j$, the transition probability

$$p(t; x_0) := \Pr \left\{ x(t; x_0) \in \mathcal{I}(\tilde{\mathcal{M}}) \right\} = [e^{\mathbf{Q}t}]_{1,j} + [e^{\mathbf{Q}t}]_{3,j}. \quad (28)$$

Figure 3 shows that as time increases, the transition probability from every initial state in $\mathcal{A}(\tilde{\mathcal{M}})$ to $\mathcal{I}(\tilde{\mathcal{M}})$ will tend to one, and the transition probability from every initial state outside of $\mathcal{A}(\tilde{\mathcal{M}})$ to $\mathcal{I}(\tilde{\mathcal{M}})$ will not tend to one. We set the initial state as δ_8^6 in the following time-domain simulation. By using the Monte-Carlo simulation method proposed in [23], a sampled trajectory of $x(t; \delta_8^6)$ is plotted in Figure 4. The simulation result intuitively shows that starting from δ_8^6 , the trajectory of $x(t; \delta_8^6)$ will eventually converge to $\mathcal{I}(\tilde{\mathcal{M}})$.

5 Conclusion

Several asymptotical stability criteria for CT-PLNs expressed in terms of the TRM were obtained. Specifically, we proved that the asymptotical stability of a CT-PLN can be verified by applying the TRM-based LIS algorithm twice. Moreover, we proved that the second calling of the LIS algorithm can be replaced by the reachability condition or the rank condition. For a non-asymptotically stable CT-PLN, a method to determine the domain of attraction was proposed. Two examples were given to illustrate the advantages of the proposed method.

The main limitation of these results is that the stability criteria are still inapplicable to large-scale CT-PLNs. The asymptotical stability of large-scale CT-PLNs warrants further research. Our future work intends to investigate the control-related problems for CT-PLNs with input nodes, such as stabilization, controllability, and optimal control.

Acknowledgements This work was supported by National Natural Science Foundation of China (Grant Nos. 61873284, 61321003).

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