Control Of Metabolic Systems Modeled with Timed Continuous Petri Nets

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Outline

1 Introduction
   Introduction

2 Basic Definitions
   Timed Continuous Petri Nets
   Controllability

3 Modelling The Metabolome
   Molecular Interpretation
   Obtaining The Metabolome Module

4 Control Law
   Regulation Control Problem
   Extended TCPN
   Solution to the RCP

5 Illustrative Controlling Metabolic System Example

6 Conclusions
Introduction

- TCPN are amenable to model biochemical reactions and cell metabolism.
- A Modelling methodology.
- Problem of reaching a required state (marking) representing a certain metabolite concentration.
Basic Definitions

Timed Continuous Petri Nets

$$TCPN = (N, \lambda, m_0).$$

$$N = (P, T, Pre, Post), m_0 \in \{\mathbb{R}^+ \cup 0\}^{\mid P \mid}.$$  

$$Pre, Post \in \{\mathbb{N} \cup 0\}^{\mid P \mid \times \mid T \mid}.$$  

$$\lambda : T \rightarrow \{\mathbb{R}^+\}^{\mid T \mid}.$$
The controlled state equation of a TCPN system is:

\[ \dot{m} = C [\Lambda \Pi (m) \cdot m - u] \]  

(1)

\[ 0 \leq u_i \leq [\Lambda \Pi (m) \cdot m]_i \]  

(2)

\[ f = \Lambda \Pi (m) \cdot m. \]  

(3)

The controlled state equation can be rewritten as:

\[ \dot{m} = C I_{c_i} \Lambda \Pi (m) \cdot m \]  

(4)

With \( 0 \leq I_{c_i} \leq 1. \)
Basic Definitions

Controllability

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Basic Definitions

Equilibrium Points

It is said that \((m_r, I_{cr})\) is an equilibrium point if
\[
\dot{m} = CI_{cr} \Pi (m_r) \cdot m_r = 0, \text{ it is}
\]
\[
m(\tau) \xrightarrow{I_{cx}} m_r
\]

and \(0 \leq I_{cr_i}(\tau) \leq 1 \ \forall \tau\).
A reaction

\[ E + S \rightarrow E + Q \]  

(6)

is represented by the next Petri net:
After a merging of elementary modules is made, pathway modules are obtained.
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Computation of $I_c$ and $I_{cr}$ such that

$$m(0) \xrightarrow{I_c} m(\tau_f) = m_r$$  \hspace{1cm} (7)

with $0 \leq I_{ci}(\tau) \leq 1$ for $0 \leq \tau < \tau_f$, and

$$m(\tau') \xrightarrow{I_{cr}} m_r$$  \hspace{1cm} (8)

with $0 \leq I_{cri}(\tau) \leq 1$ for $\tau' \geq \tau_f$. 

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Control Law

Extended TCPN

\[
\dot{m}_x = \begin{bmatrix} \dot{m} \\ \dot{m}_a \end{bmatrix} = \begin{bmatrix} CIc\Lambda\Pi(m) \cdot m \\ Ic\Lambda\Pi(m) \cdot m \end{bmatrix}
\]

\[
m_r = m_0 + C\sigma_r
\]
Control Law

Solution to the RCP

\[ e = m_r - m \]  \hspace{1cm} (11)

\[ e_a = \sigma_r - m_a \]  \hspace{1cm} (12)

\[ I_{ci} = \begin{cases} 
1 & \text{if } m_a[i] < \sigma_r[i] \\
0 & \text{otherwise}
\end{cases} \]  \hspace{1cm} (13)
Solution to the RCP

Suppose that it occurs $m_a(\tau_1) = \sigma_1$ and $\sigma_1[i] < \sigma_r[i] \ \forall i$, now from $m_1 = m_0 + C\sigma_1$ we have

$$m_r = m_1 + C(\sigma_r - \sigma_1) = m_1 + C(\sigma_{r2}) \quad (14)$$

Since $\sigma_{r2} > 0$ then it is feasible and the same procedure can be applied in succession.

$$\begin{bmatrix} \dot{m} \\ \dot{m}_a \end{bmatrix} = \begin{bmatrix} C I_c \Lambda \Pi (m) \cdot m \\ I_c \Lambda \Pi (m) \cdot m \end{bmatrix} \quad (15)$$

$$I_{c_i} = \begin{cases} 
1 & \text{if } m_a[i] < \sigma_r[i] \\
0 & \text{otherwise}
\end{cases} \quad (16)$$
Illustrative Controlling Metabolic System Example

Example

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Example

Let a metabolome model be the system $TCPN = (N, \lambda, m_0)$ with $\Lambda = \text{diag}(2, 3, 4, 1)$ and $m_0 = \begin{bmatrix} 100 & 80 & 100 & 50 & 70 & 5 & 3 & 2 & 4 \end{bmatrix}^T$. Let $m_r = \begin{bmatrix} 95 & 70 & 60 & 65 & 110 & 5 & 3 & 2 & 4 \end{bmatrix}^T$ be a required marking.

$$\sigma_r = \begin{bmatrix} 30 & 40 & 25 & 0 \end{bmatrix}^T$$

Notice that from $\tau = 0$ to $\tau = \tau_f \approx 4.5$ occurs the transitory dynamics, and for $\tau > \tau_f$ the steady state is reached.
Illustrative Controlling Metabolic System Example

Example

![Graph showing metabolic system example](image-url)
Example
Conclusions

This work presented a model methodology to capture the metabolome behavior. It uses a bottom-up approach where each individual biochemical reaction is modeled by elementary TCPN modules and, afterwards, all the modules are merged into a single one to capture the whole metabolome behavior.

This work also presented the problem of reaching a required metabolome state. The solution to this problem are the instantaneous reaction velocities that are realizable in biological system.
Present results are being applied to optimize metabolome fermentation in the production of tequila and to biofuels generation.

Future perspective involves introduction of stochastic modelling and merging the metabolome with the signaling and genetic networks.