Control Of Metabolic Systems Modeled with Timed Continuous Petri Nets

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Outline

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.

Timed Continuous Petri Nets

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

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

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

$$\lambda : T \to \{\mathbb{R}^+\}^{|T|}$$

Timed Continuous Petri Nets

The controlled state equation of a $TCPN$ system is:

$$\dot{m} = C\left[\Lambda\Pi\left(m\right)\cdot m - u\right] \tag{1}$$

$$0 \leq u_i \leq \left[\Lambda\Pi\left(m\right)\cdot m\right]_i \tag{2}$$

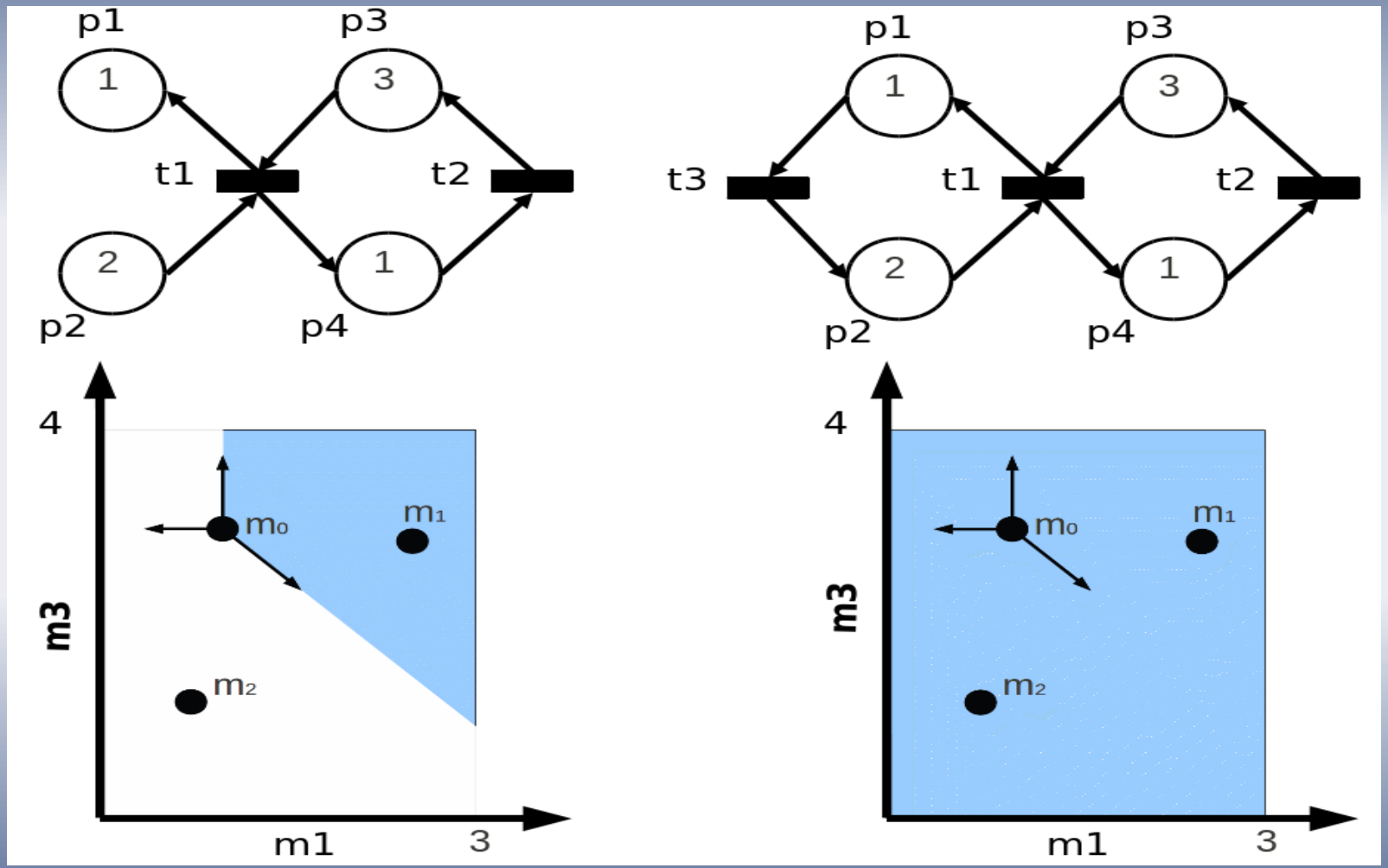
$$f = \Lambda\Pi\left(m\right)\cdot m. \tag{3}$$

The controlled state equation can be rewritten as:

$$\dot{m} = CI_c\Lambda\Pi\left(m\right)\cdot m \tag{4}$$

With $0 \leq I_{c_i} \leq 1$.

Controllability



Equilibrium Points

It is said that (m_r, I_{cr}) is an equilibrium point if $\dot{m} = CI_{cr}\Lambda\Pi\left(m_r\right) \cdot m_r = 0$, it is

$$m(\tau) \overset{I_{cr}}{\rightarrow} m_r \tag{5}$$

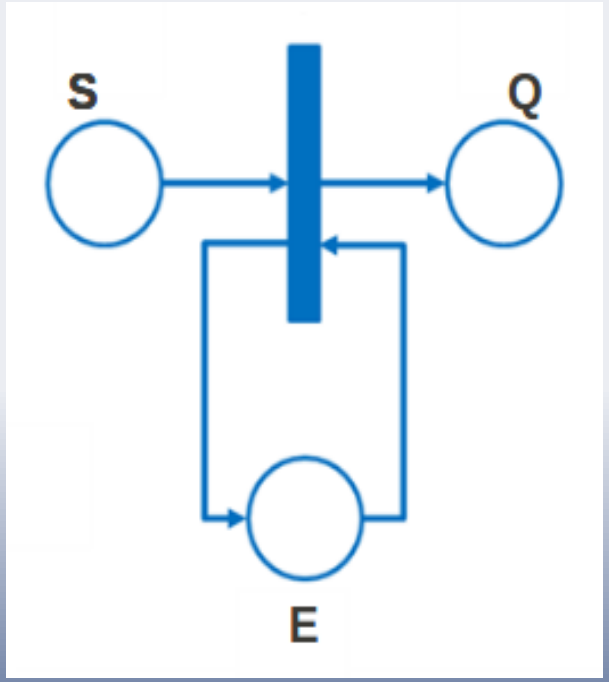
and $0 \leq I_{cr_i}(\tau) \leq 1 \ \forall\tau$.

Representing Reactions

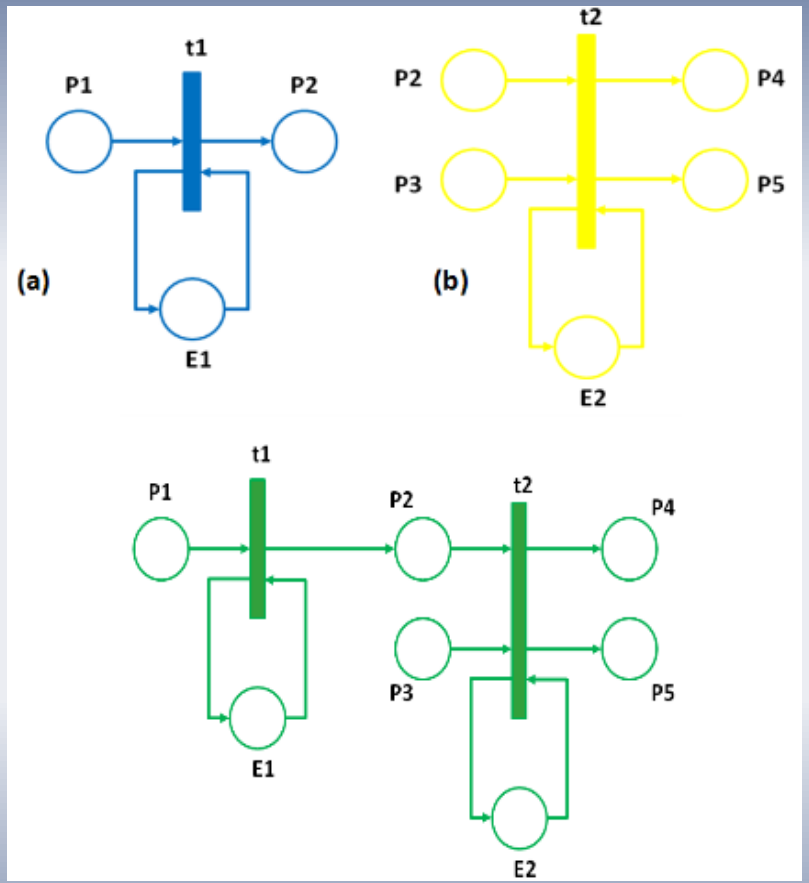
A reaction

$$E + S \rightarrow E + Q \tag{6}$$

is represented by the next Petri net:

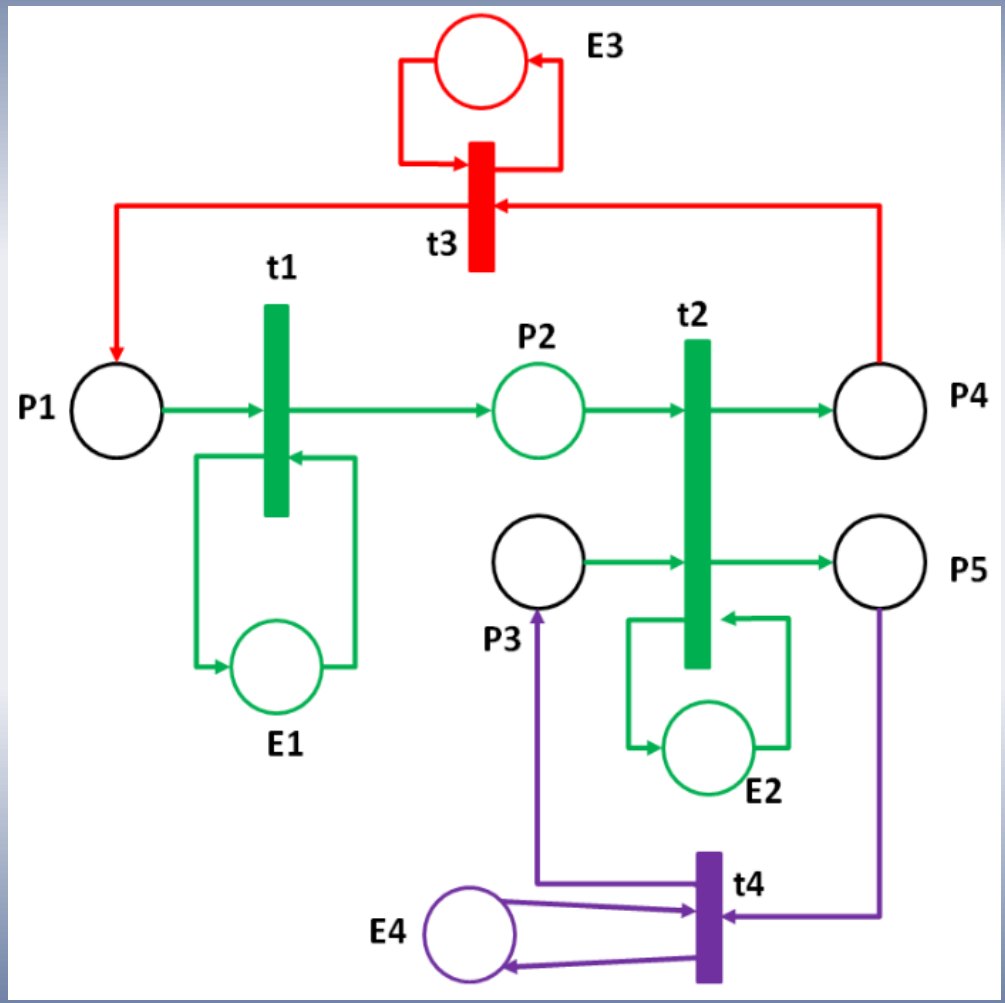


Merging Elementary Modules



After a merging of elementary modules is made, pathway modules are obtained.

Metabolome Module



Regulation Control Problem

Computation of I_c and I_{cr} such that

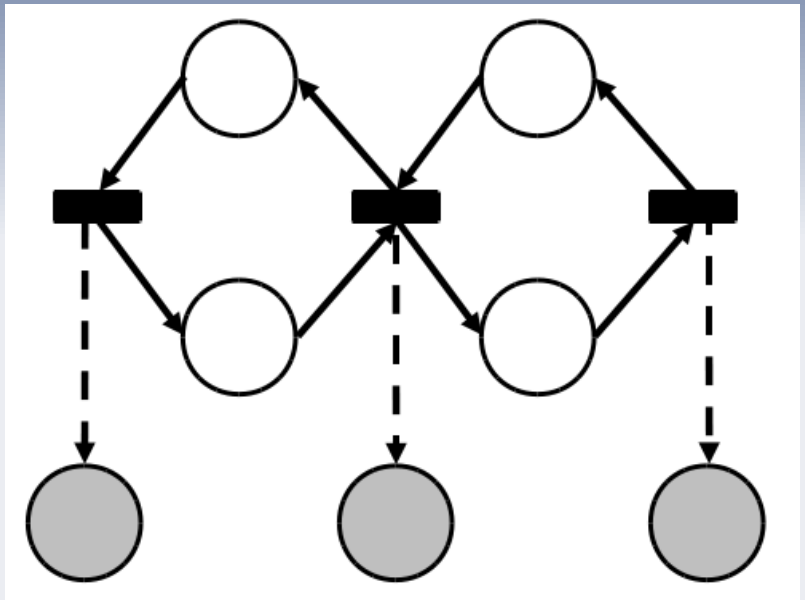
$$m(0) \xrightarrow{I_c} m(\tau_f) = m_r \tag{7}$$

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

$$m(\tau') \xrightarrow{I_{cr}} m_r \tag{8}$$

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

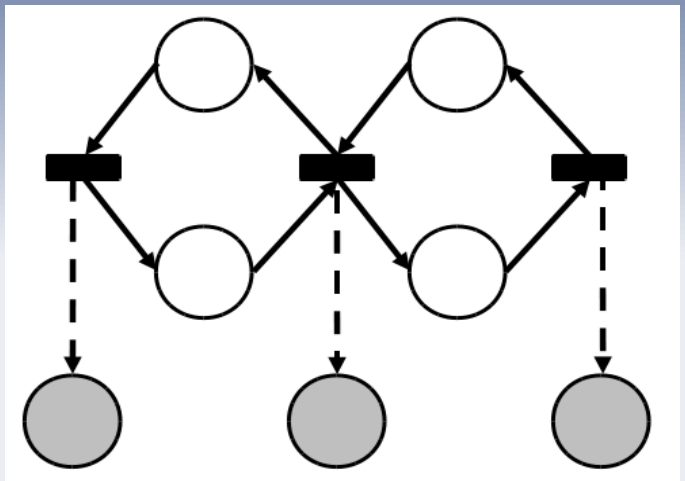
Extended TCPN



$$\dot{m}_x = \begin{bmatrix} \dot{m} \\ \dot{m}_a \end{bmatrix} = \begin{bmatrix} CI_c\Lambda\Pi(m)\cdot m \\ I_c\Lambda\Pi(m)\cdot m \end{bmatrix} \quad (9)$$

$$m_r = m_0 + C\sigma_r \quad (10)$$

Solution to the RCP



$$e = m_r - m \tag{11}$$

$$e_a = \sigma_r - m_a \tag{12}$$

$$I_{c_i} = \begin{cases} 1 & \text{if } m_a[i] < \sigma_r[i] \\ 0 & otherwhise \end{cases} \tag{13}$$

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

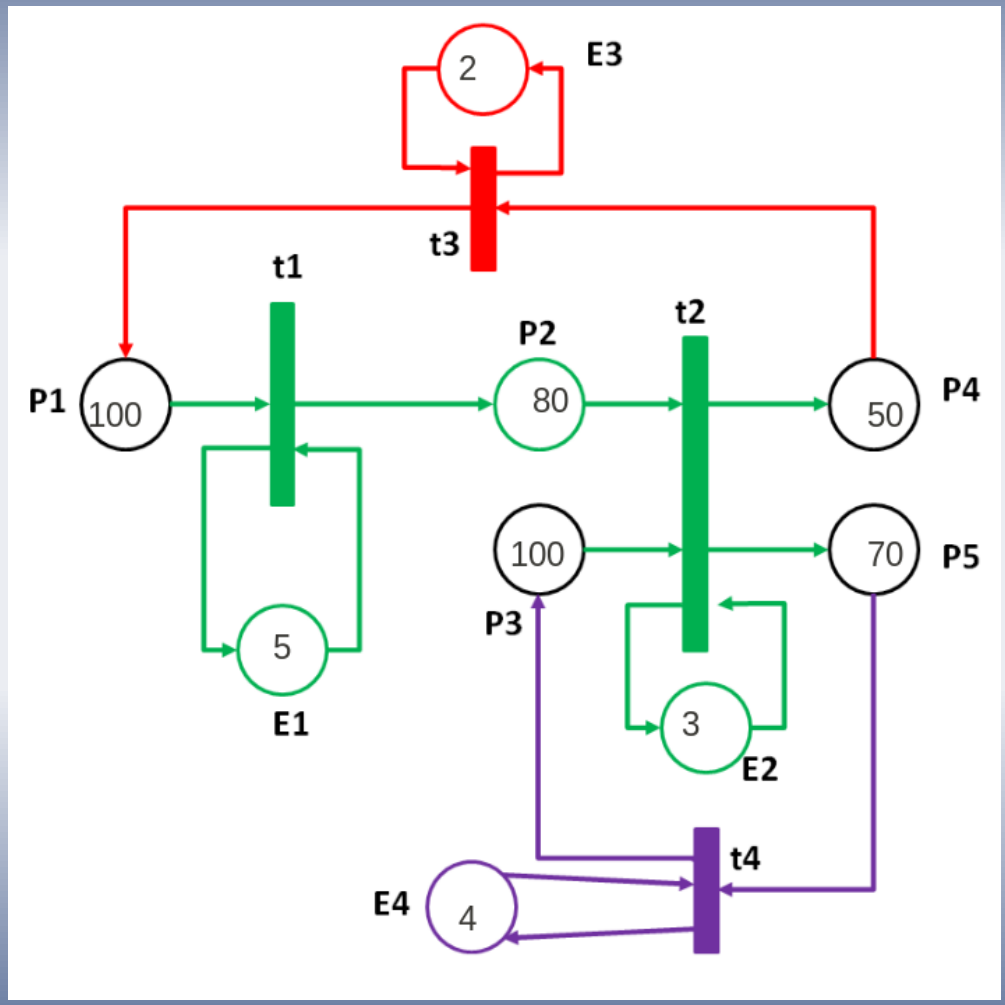
$$m_r = m_1 + C(\sigma_r - \sigma_1) = m_1 + C(\sigma_{r2}) \tag{14}$$

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

$$\dot{m}_x = \begin{bmatrix} \dot{m} \\ \dot{m}_a \end{bmatrix} = \begin{bmatrix} CI_c\Lambda\Pi\,(m)\cdot m \\ I_c\Lambda\Pi\,(m)\cdot m \end{bmatrix} \tag{15}$$

$$I_{c_i} = \begin{cases} 1 & \text{if } m_a\,[i] < \sigma_r\,[i] \\ 0 & otherwhise \end{cases} \tag{16}$$

Example



Example

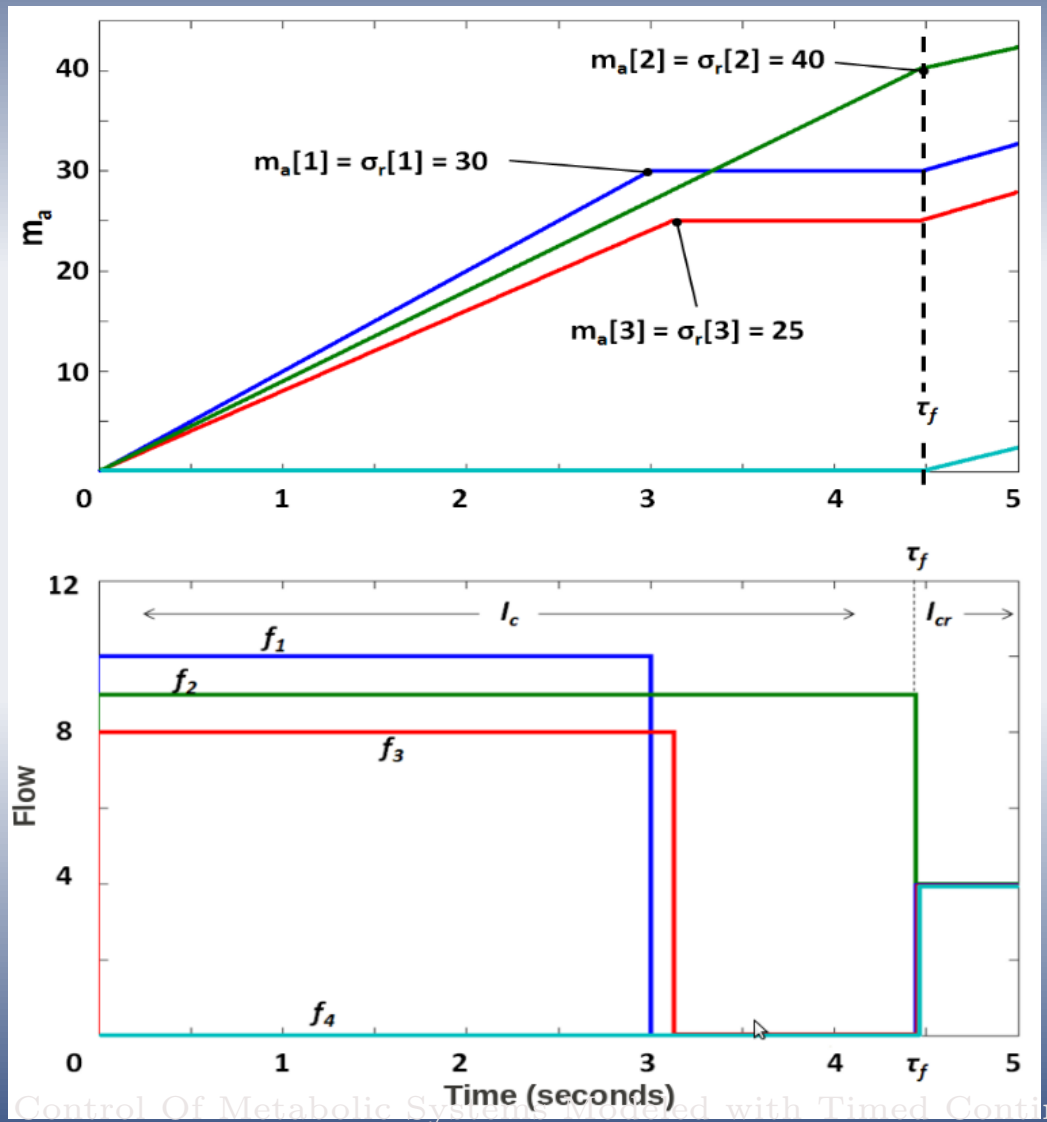
Example

Let a metabolome model be the system $TCPN = (N, \lambda, m_0)$ with $\Lambda = diag\,(2, 3, 4, 1)$ 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.

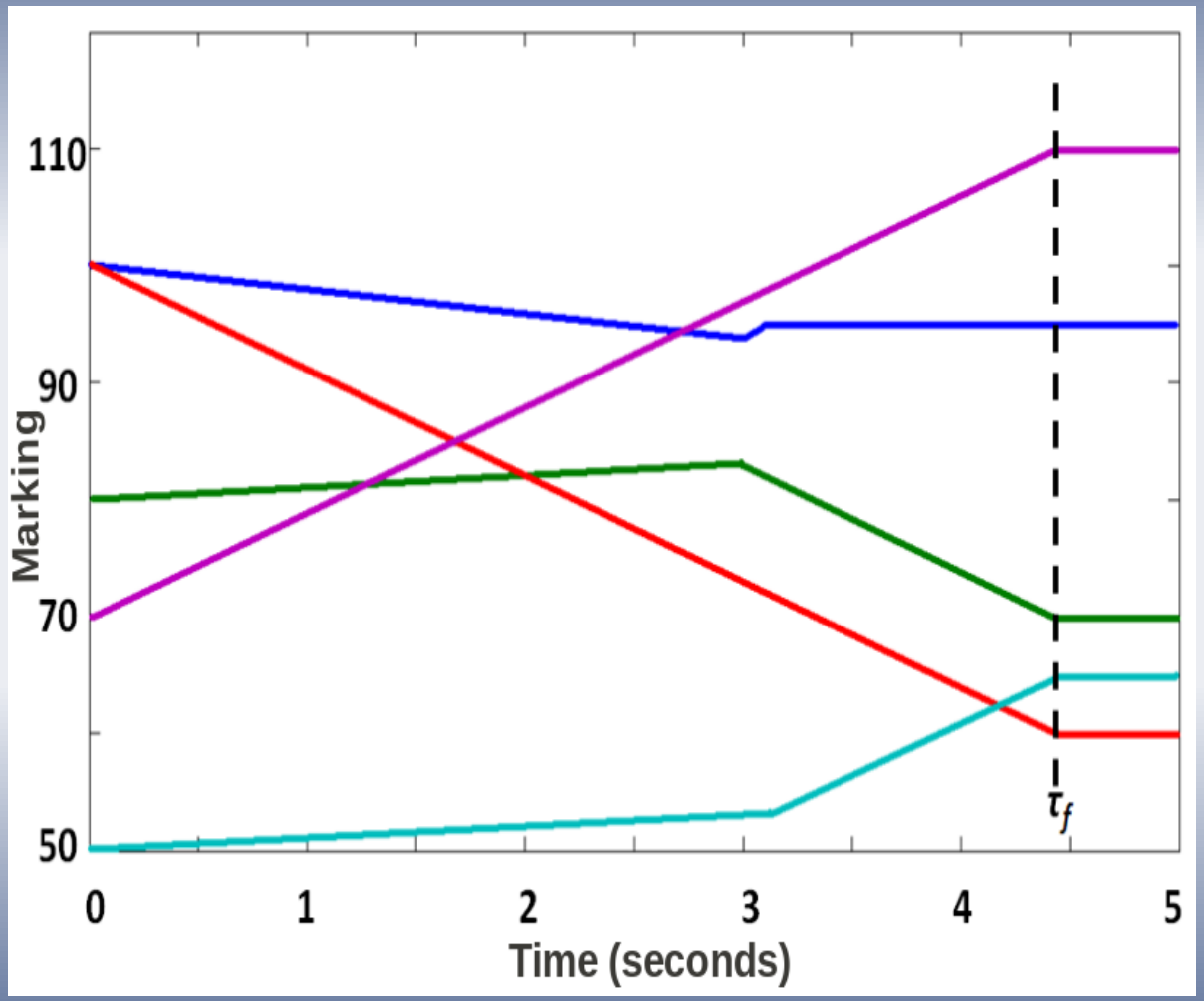
$$\sigma_r = \begin{bmatrix} 30 & 40 & 25 & 0 \end{bmatrix}^T$$

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.

Example


$m_a[2] = \sigma_r[2] = 40$
$m_a[1] = \sigma_r[1] = 30$
$m_a[3] = \sigma_r[3] = 25$
m_a
τ_f
l_c
l_{cr}
f_1
f_2
f_3
f_4
Flow
Time (seconds)

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.

Actual Work and Future Perspective

- 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.