Lecture 2
Graphical Representation of Biochemical Networks: Petri Nets

Luca Bortolussi\textsuperscript{1}  Alberto Policriti\textsuperscript{2}

\textsuperscript{1}Dipartimento di Matematica ed Informatica
Università degli studi di Trieste
Via Valerio 12/a, 34100 Trieste.
luca@dmi.units.it

\textsuperscript{2}Dipartimento di Matematica ed Informatica
Università degli studi di Udine
Via delle Scienze 206, 33100 Udine.
policriti@dimi.uniud.it

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Summary

1. Chemical Reactions
2. Graphical Representations
3. Petri Nets
Material from chapter 1 and 2 of:

Stochastic Modelling for Systems Biology

Darren J. Wilkinson
Formal representation of chemical reactions

- precise
- qualitative *and* quantitative
- suitable to introduce *discrete* and *stochastic* ingredients

We begin with

**Network of coupled chemical reactions**

\[ m_1 R_1 + m_2 R_2 + \ldots + m_r R_r \rightarrow n_1 P_1 + n_2 P_2 + \ldots + n_p P_p \]

**Definitions**

1. \( R_i \)'s: reactants;
2. \( P_j \)'s: products;
3. \( m_i \)'s and \( n_j \)'s: stoichiometries.
Formal representation of chemical reactions

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**Definitions**

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Example: (procaryote) gene transcription

\[ p + \text{RNAP} \rightarrow p \cdot \text{RNAP} \]

\[ p \cdot \text{RNAP} \rightarrow p + \text{RNAP} + r. \]
Example: (procaryote) gene transcription

\[ p + \text{RNAP} \rightarrow p \cdot \text{RNAP} \]
\[ p \cdot \text{RNAP} \rightarrow p + \text{RNAP} + r. \]
Reactants and Products need not be different: Dimerisation of a protein $P$

$$2P \rightarrow P_2$$

if reversible:

$$2P \leftrightarrow P_2$$

Not every reaction is modelled

Some product “pops out” mysteriously

(detail?)

rates are missing
Example: mRNA translation

\[ r + \text{Rib} \leftrightarrow r \cdot \text{Rib} \]
\[ r \cdot \text{Rib} \rightarrow r + \text{Rib} + \text{Pu} \]
\[ \text{Pu} \rightarrow P \]
Example: mRNA translation

\[ r + \text{Rib} \leftrightarrow r \cdot \text{Rib} \]
\[ r \cdot \text{Rib} \rightarrow r + \text{Rib} + P_u \]
\[ P_u \rightarrow P \]
Example: ribonuclease mRNA degradation

\[ r + \text{RNase} \rightarrow r \cdot \text{RNase} \]
\[ r \cdot \text{RNase} \rightarrow \text{RNase} \]
Example: ribonuclease mRNA degradation

\[ r + \text{RNase} \rightarrow r \cdot \text{RNase} \]
\[ r \cdot \text{RNase} \rightarrow \text{RNase} \]
Example: negative regulation

\[ g + R \leftrightarrow g \cdot R \]
\[ g + \text{RNAP} \leftrightarrow g \cdot \text{RNAP} \]
\[ g \cdot \text{RNAP} \rightarrow g + \text{RNAP} + r \]
Example: negative regulation

\[ g + R \leftrightarrow g \cdot R \]

\[ g + RNAP \leftrightarrow g \cdot RNAP \]

\[ g \cdot RNAP \rightarrow g + RNAP + r \]
The order of reactions

Reactions do not execute in linear order

The “interesting” ingredients come up when loops are present
Example: negative auto-regulation

\[ g + P_2 \rightleftharpoons g \cdot P_2 \]
\[ g \rightarrow g + r \]
\[ r \rightarrow r + P \]

\[ 2P \rightleftharpoons P_2 \]
\[ r \rightarrow \emptyset \]
\[ P \rightarrow \emptyset \]
Example: negative auto-regulation

\[ g + P_2 \leftrightarrow g \cdot P_2 \]
\[ g \rightarrow g + r \]
\[ r \rightarrow r + P \]

2P \leftrightarrow P_2

r \rightarrow \emptyset

P \rightarrow \emptyset
Informal diagram

Chemical Reactions
Graphical Representations
Petri Nets
Chemical reactions

\[
g + P_2 \leftrightarrow g \cdot P_2 \\
g \rightarrow g + r \\
r \rightarrow r + P \\
2P \leftrightarrow P_2 \\
r \rightarrow \emptyset \\
P \rightarrow \emptyset
\]
Chemical reactions

\[
g + P_2 \leftrightarrow g \cdot P_2 \quad \text{Repression}
\]
\[
g \rightarrow g + r \quad \text{Transcription}
\]
\[
r \rightarrow r + P \quad \text{Translation}
\]
\[
2P \leftrightarrow P_2 \quad \text{Dimerisation}
\]
\[
r \rightarrow \emptyset \quad \text{mRNA degradation}
\]
\[
P \rightarrow \emptyset \quad \text{Protein degradation}
\]
Chemical Reactions

Graphical Representations

Petri Nets

Definitions

Definition

A directed graph (digraph) $G$ is $(V, E)$ where

1. $V = \{v_1, \ldots, v_n\};$
2. $E \subseteq \{(v_i, v_j) \mid v_i, v_j \in V\} = V \times V.$

Definition

1. $G$ is **simple** if there are no self-loops and no repeated edges.
2. $G$ is **bipartite** if there exists $V_1, V_2 \subset V$ such that $V = V_1 \cup V_2, V_1 \cap V_2 = \emptyset,$ and $(v_i, v_j) \Rightarrow (v_i \in V_1 \iff v_j \in V_2);$ 
3. $G$ is **weighted** if every edge has a weight.

Why *simple*, *bipartite*, and *weighted* graphs?
Definitions

**Definition**

A **directed graph (digraph)** \( G \) is \((V, E)\) where

- \( V = \{v_1, \ldots, v_n\} \);
- \( E \subseteq \{\langle v_i, v_j \rangle \mid v_i, v_j \in V\} = V \times V \).

**Definition**

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2. **\( G \) is bipartite** if there exists \( V_1, V_2 \subset V \) such that
   \( V = V_1 \cup V_2, V_1 \cap V_2 = \emptyset \), and
   \( \langle v_i, v_j \rangle \Rightarrow (v_i \in V_1 \iff v_j \in V_2) \);
3. **\( G \) is weighted** if every edge has a **weight**.

Why *simple*, *bipartite*, and *weighted* graphs?
Definitions

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A directed graph (digraph) $G$ is $(V, E)$ where

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3. $G$ is **weighted** if every edge has a weight.

Why **simple**, **bipartite**, and **weighted** graphs?
Reaction graphs: the discrete ingredient.

- We will work with *species* and *reactions* ⇒ simple and bipartite graphs.
- We want to keep track of *stoichiometries* ⇒ weighted graphs.
Place/Transition Petri Nets

\[ g + P_2 \leftrightarrow g \cdot P_2 \]
\[ g \rightarrow g + r \]
\[ r \rightarrow r + P \]
\[ 2P \leftrightarrow P_2 \]
\[ r \rightarrow \emptyset \]
\[ P \rightarrow \emptyset \]

Repression
Transcription
Translation
Dimerisation
mRNA degradation
Protein degradation
### P/T Petri Nets: alternative representation

<table>
<thead>
<tr>
<th>Species</th>
<th>Reactants ($Pre$)</th>
<th>Products ($Post$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$g \cdot P_2$</td>
<td>$g$</td>
</tr>
<tr>
<td>Repression</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Reverse repression</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Transcription</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Translation</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Dimerisation</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dissociation</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>mRNA degradation</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Protein degradation</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>
P/T Petri Net: marking
P/T Petri Net: firing (two reaction)

\[ g + P_2 \rightarrow g \cdot P_2 \]  
\[ r \rightarrow r + P \]  
Repression  
Translation
P/T Petri Net: firing (two reaction)

\[
g + P_2 \rightarrow g \cdot P_2 \quad \text{Repression}
\]

\[
r \rightarrow r + P \quad \text{Translation}
\]
### P/T Petri Net marking: alternative representation

<table>
<thead>
<tr>
<th>Species</th>
<th>num. of tokens</th>
</tr>
</thead>
<tbody>
<tr>
<td>$g \cdot P_2$</td>
<td>0</td>
</tr>
<tr>
<td>$g$</td>
<td>1</td>
</tr>
<tr>
<td>$r$</td>
<td>2</td>
</tr>
<tr>
<td>$P$</td>
<td>10</td>
</tr>
<tr>
<td>$P_2$</td>
<td>12</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
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<tbody>
<tr>
<td>$g \cdot P_2$</td>
<td>1</td>
</tr>
<tr>
<td>$g$</td>
<td>0</td>
</tr>
<tr>
<td>$r$</td>
<td>2</td>
</tr>
<tr>
<td>$P$</td>
<td>11</td>
</tr>
<tr>
<td>$P_2$</td>
<td>11</td>
</tr>
</tbody>
</table>
P/T Petri Nets: definition

**Definition**

A P/T Petri net is

\[ N = \langle P, T, Pre, Post, M \rangle \]

where \( P \) is the vector of **Places**, \( T \) is the vector of **Transitions**, \( Pre \) and \( Post \) are the labels on arcs (remember: bipartite graph) and \( M \) is the initial marking vector.

Notation: \(|P| = u, |T| = v\), and both \( Pre \) and \( Post \) are \( v \times u \) matrices.
P/T Petri Nets: definition

Definition

A P/T Petri net is

\[ N = \langle P, T, \text{Pre}, \text{Post}, M \rangle \]

where \( P \) is the vector of \text{Places}, \( T \) is the vector of \text{Transitions}, \( \text{Pre} \) and \( \text{Post} \) are the labels on arcs (remember: bipartite graph) and \( M \) is the initial marking vector.

Notation: \(|P| = u, |T| = v\), and both \( \text{Pre} \) and \( \text{Post} \) are \( v \times u \) matrices.
**P/T Petri Nets: matrix representation (example)**

\[
P = \begin{pmatrix} g \cdot P_2 \\ g \\ r \\ P \\ P_2 \end{pmatrix} \quad T = \begin{pmatrix} \text{Repression} \\ \text{Reverse repression} \\ \text{Transcription} \\ \text{Translation} \\ \text{Dimerisation} \\ \text{Dissociation} \\ \text{mRNA degradation} \\ \text{Protein degradation} \end{pmatrix} \quad M = \begin{pmatrix} 0 \\ 1 \\ 2 \\ 10 \\ 12 \end{pmatrix}
\]

\[
Pre = \begin{pmatrix} 0 & 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 2 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 & 0 \end{pmatrix} \quad Post = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 2 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}
\]
Matrices!

The *dynamics* can be represented by ... a matrix:

\[
A = Post - Pre = \begin{pmatrix}
1 & -1 & 0 & 0 & -1 \\
-1 & 1 & 0 & 0 & 1 \\
0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & -2 & 1 \\
0 & 0 & 0 & 2 & -1 \\
0 & 0 & -1 & 0 & 0 \\
0 & 0 & 0 & -1 & 0 \\
\end{pmatrix}
\]

... or equivalently by:

\[
S = A'
\]

Computation can be performed by matrix calculus

**Computing the markings**

If we represent the transition that have taken place (in parallel) by a vector, we can multiply and sum matrices to compute the new marking.

**Example**

A Repression reaction and a Translation reaction can be represented by $r = (1, 0, 0, 1, 0, 0, 0, 0)'$ where:

<table>
<thead>
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In general:

$$\tilde{M} = M + Sr$$
### Invariants

**Definition**

A *P*-invariant is a non-zero vector \( y \) such that \( Ay = 0 \).

**P-invariant as conservation laws**

in the example \((1, 1, 0, 0, 0)\)' is a *P*-invariant and corresponds to the observation that

\[
g \cdot P_2 + g = \text{const}.
\]

**Proof**

\[
y'\tilde{M} - y'M = y'(\tilde{M} - M)
= y'Sr
= (S'y)'r
= (Ay)'r
= 0
\]
Invariants

**Definition**

A *P-invariant* is a non-zero vector $y$ such that $Ay = 0$.

**P-invariant as conservation laws**

In the example $(1, 1, 0, 0, 0)'$ is a *P*-invariant and corresponds to the observation that

$$g \cdot P_2 + g = \text{const.}$$

**proof**

\[
y' \tilde{M} - y'M &= y' (\tilde{M} - M) \\
&= y' Sr \\
&= (S'y)'r \\
&= (Ay)'r \\
&= 0
\]
**Definition**

A *T-invariant* is a non-zero vector $x$ such that $Sx = 0$.

*T-invariants are *canceling cycles of actions* in the example $(1, 1, 0, 0, 0, 0, 0)'$ is a *T*-invariant and corresponds to the observation that a Repression and a Reverse repression do cancel out.

**proof**

Use again:

$$\tilde{M} = M + Sr.$$
**Definition**

A *T*-invariant is a non-zero vector $x$ such that $Sx = 0$.

**T*-invariants are *canceling cycles* of actions

in the example $(1, 1, 0, 0, 0, 0, 0)'$ is a *T*-invariant and corresponds to the observation that a Repression and a Reverse repression do cancel out.

**proof**

Use again:

$$\tilde{M} = M + Sr.$$
invariants correspond to loops in the dynamics: are important;

rates are missing and their addition is the way to introduce the stochastic ingredient;

(stochastic) quantitative aspects enter the picture via markings. It is not the only way;

P/T Petri Nets are neat and compact but they are not modular: transitions link everything together.