Graphical Representation of Biochemical Networks.
(and Petri Nets)

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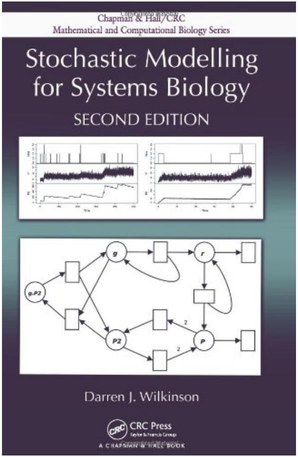
Summary

Material from chapter 1 ad 2 of:



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.*

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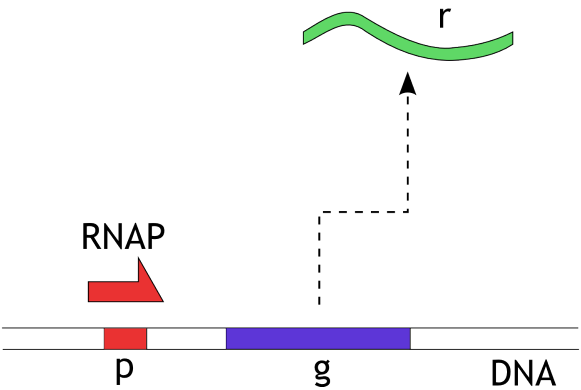
Example: (procaryote) gene transcription



$$p + RNAP \to p \cdot RNAP$$
$$p \cdot RNAP \to p + RNAP + r.$$

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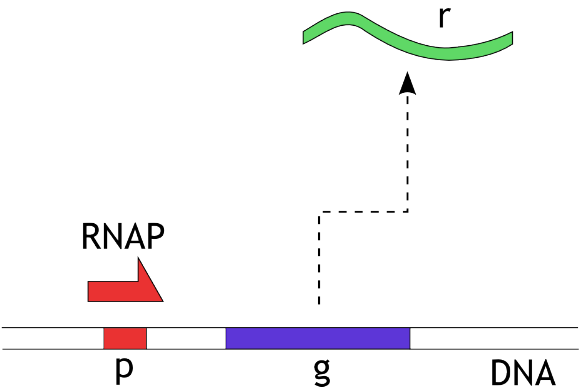

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Details

Reactants and Products need not be different: Dimerisation of a protein P

$$2P \to P_2$$

if reversible:

$$2P \leftrightarrow P_2$$

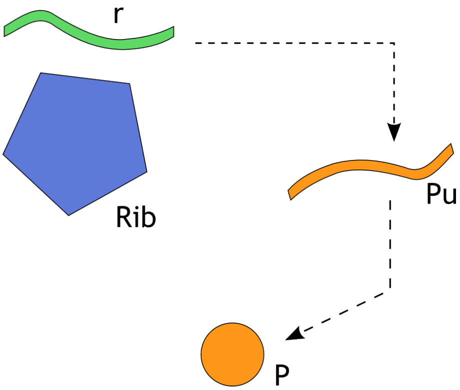
Not every reaction is modelled

Some product "pops out" mysteriously

(detail?)

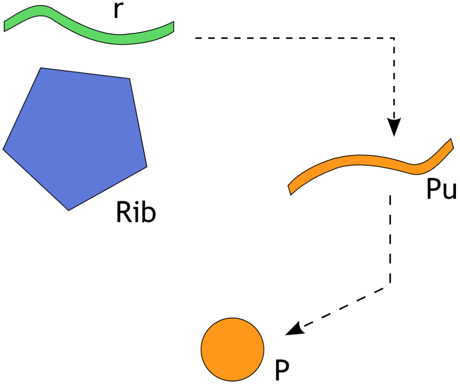
rates are missing

Example: mRNA translation



$$r + Rib \leftrightarrow r \cdot Rib$$
$$r \cdot Rib \rightarrow r + Rib + P_u$$
$$P_u \rightarrow P$$

Example: mRNA translation



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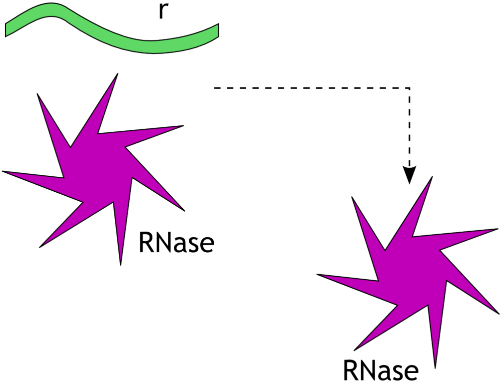
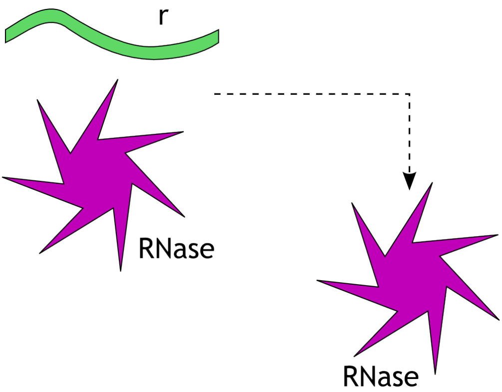
Example: ribonuclease mRNA degradation



$$r + RNase \to r \cdot RNase$$
$$r \cdot RNase \to RNase$$

Example: ribonuclease mRNA degradation



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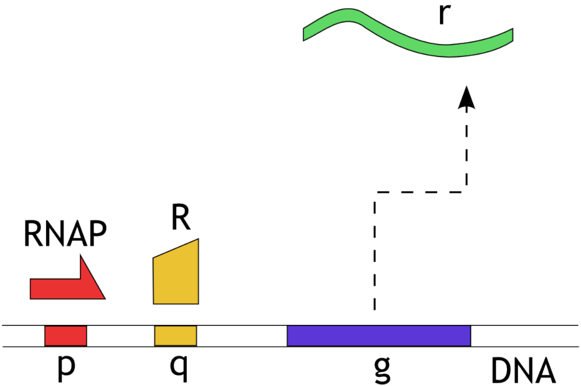
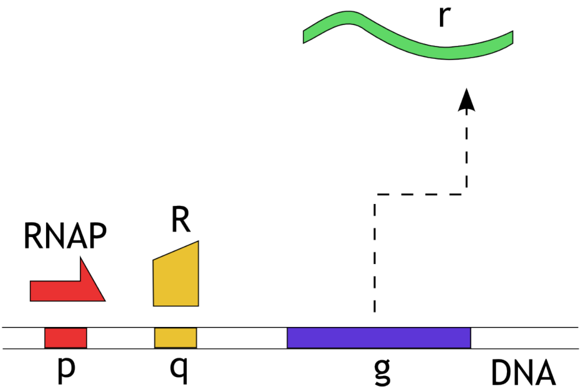
Example: negative regulation



$$g + R \leftrightarrow g \cdot R$$
$$g + RNAP \leftrightarrow g \cdot RNAP$$
$$g \cdot RNAP \rightarrow g + RNAP + r$$

Example: negative regulation



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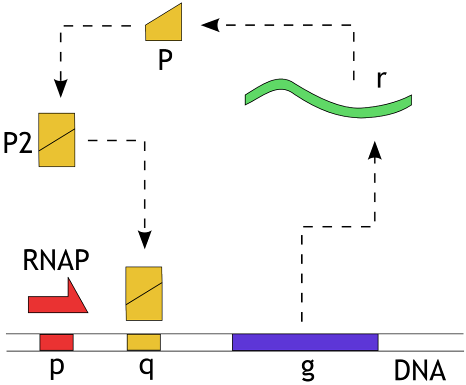
The order of reactions

Reactions do not execute in linear order

The “interesting” ingredients come up when loops are present

Example: negative auto-regulation



$$g + P_2 \leftrightarrow g \cdot P_2$$
$$g \rightarrow g + r$$
$$r \rightarrow r + P$$

$$2P \leftrightarrow P_2$$
$$r \rightarrow \emptyset$$
$$P \rightarrow \emptyset$$

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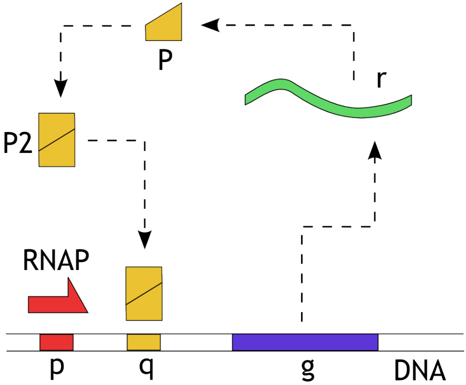

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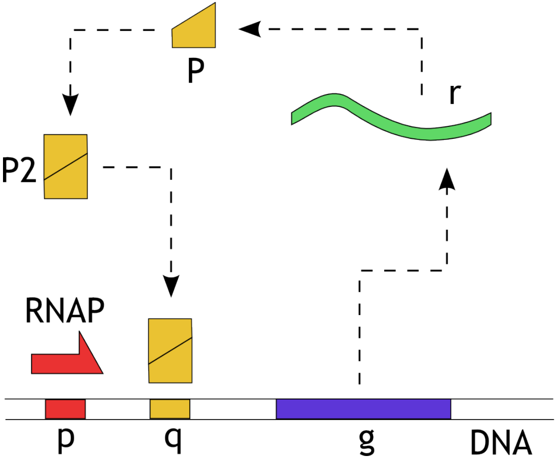
Informal diagram



Chemical reactions

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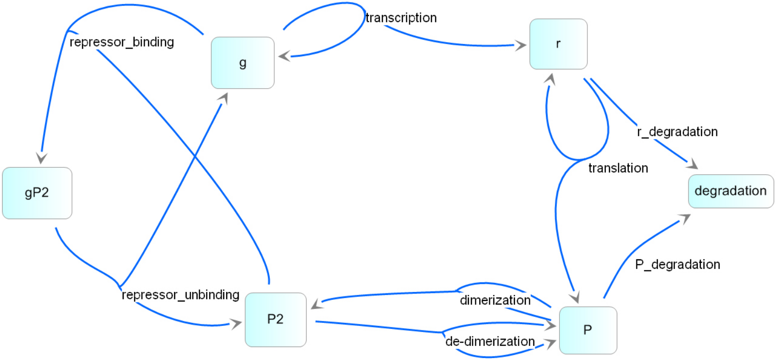
Chemical reactions

$g + P_2 \leftrightarrow g \cdot P_2$	Repression
$g \rightarrow g + r$	Transcription
$r \rightarrow r + P$	Translation
$2P \leftrightarrow P_2$	Dimerisation
$r \rightarrow \emptyset$	mRNA degradation
$P \rightarrow \emptyset$	Protein degradation

Fluxes


repressor_binding
g
transcription
r
r_degradation
translation
degradation
gP2
P_degradation
repressor_unbinding
P2
dimerization
P
de-dimerization

Definitions

Definition

A directed graph (digraph) $\mathcal{G}$ 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

1. $\mathcal{G}$ is simple if there are no self-loops and no repeated edges.
2. $\mathcal{G}$ 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 $\langle v_i, v_j \rangle \Rightarrow (v_i \in V_1 \Leftrightarrow v_j \in V_2)$;
3. $\mathcal{G}$ is weighted if every edge has a *weight*.

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

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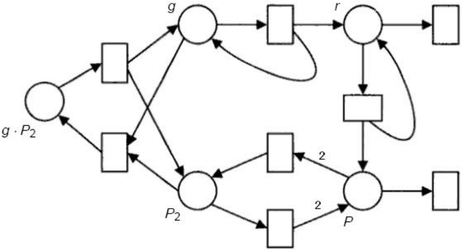
Why *simple*, *bipartite*, and *weighted* graphs?

Reaction 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



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$r \rightarrow r + P$	Translation
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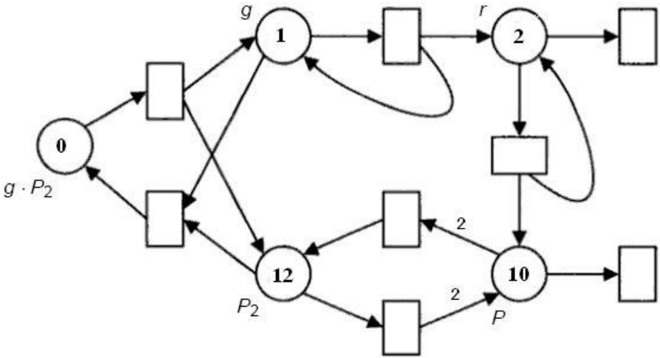
$P \rightarrow \emptyset$	Protein degradation

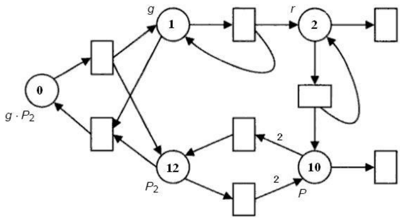
P/T Petri Nets: alternative representation

	Reactants (*Pre*)					Products (*Post*)				
Species	$g \cdot P_2$	g	r	P	P_2	$g \cdot P_2$	g	r	P	P_2
Repression		1			1	1				
Reverse repression	1						1			1
Transcription		1					1	1		
Translation			1					1	1	
Dimerisation				2						1
Dissociation					1				2	
mRNA degradation			1							
Protein degradation				1						

P/T Petri Net: marking



P/T Petri Net: firing (*two* reaction)



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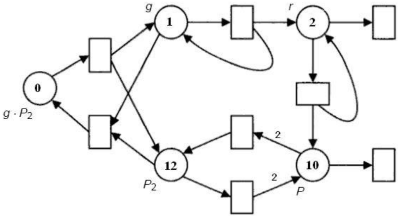

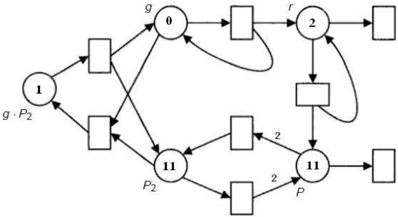

$g + P_2 \to g \cdot P_2$	Repression
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P/T Petri Net marking: alternative representation

Species	num. of tokens
$g \cdot P_2$	0
g	1
r	2
P	10
P_2	12

Species	num. of tokens
$g \cdot P_2$	1
g	0
r	2
P	11
P_2	11

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.

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P/T Petri Nets by matrices (example)

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

$$Pre = \begin{pmatrix} 0 & 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 2 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \end{pmatrix} \quad Post = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 2 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

Matrices!

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

$$A \quad = Post - Pre = \begin{pmatrix} 1 & -1 & 0 & 0 & -1 \\ -1 & 1 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & -2 & 1 \\ 0 & 0 & 0 & 2 & -1 \\ 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & -1 & 0 \end{pmatrix}$$

... or equivalently by:

$$S \quad = \quad A'$$

Names: A reaction matrix, S stoichiometry matrix.

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:

Reactions	num. of transitions
Repression	1
Reverse repression	0
Transcription	0
Translation	1
Dimerisation	0
Dissociation	0
mRNA degradation	0
Protein degradation	0

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

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

$$g \cdot P_2 + g = const.$$

Proof

$$\begin{aligned} y'\tilde{M} - y'M &= y'(\tilde{M} - M) \\ &= y'Sr \\ &= (S'y)'r \\ &= (Ay)'r \\ &= 0 \end{aligned}$$

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T-invariants

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T-invariants are *canceling cycles* of actions

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Use again:

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PROOF

Use again:

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

... NEXT

- 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.