Models and Languages for Computational Systems Biology

Lecture 1: Systems and Models

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The University of Edinburgh

Monday 11 January 2010
Semester 2 Week 1

Systems Biology

Biology is the study of living organisms; Systems Biology is the study of the dynamic processes that take place within those organisms.

In particular:

- Interaction between processes;
- Behaviour emerging from such interaction; and
- Integration of component behaviours.

Systems Biology

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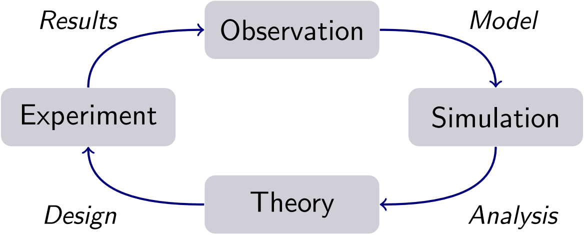
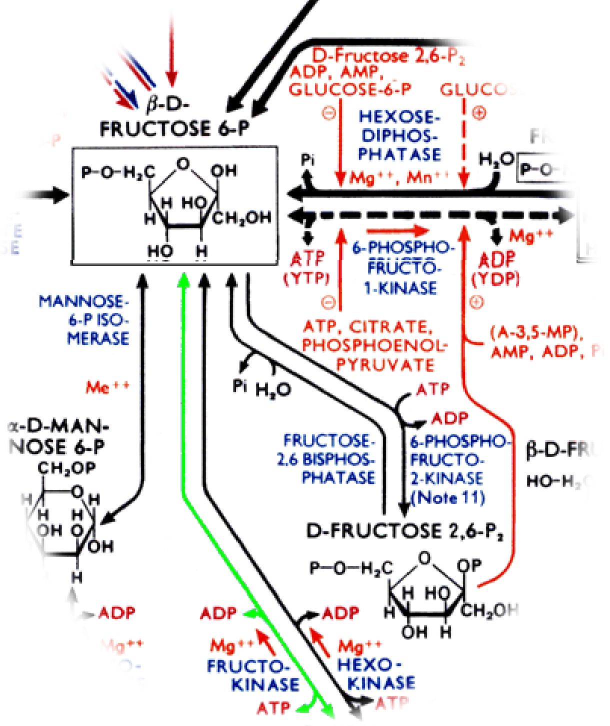
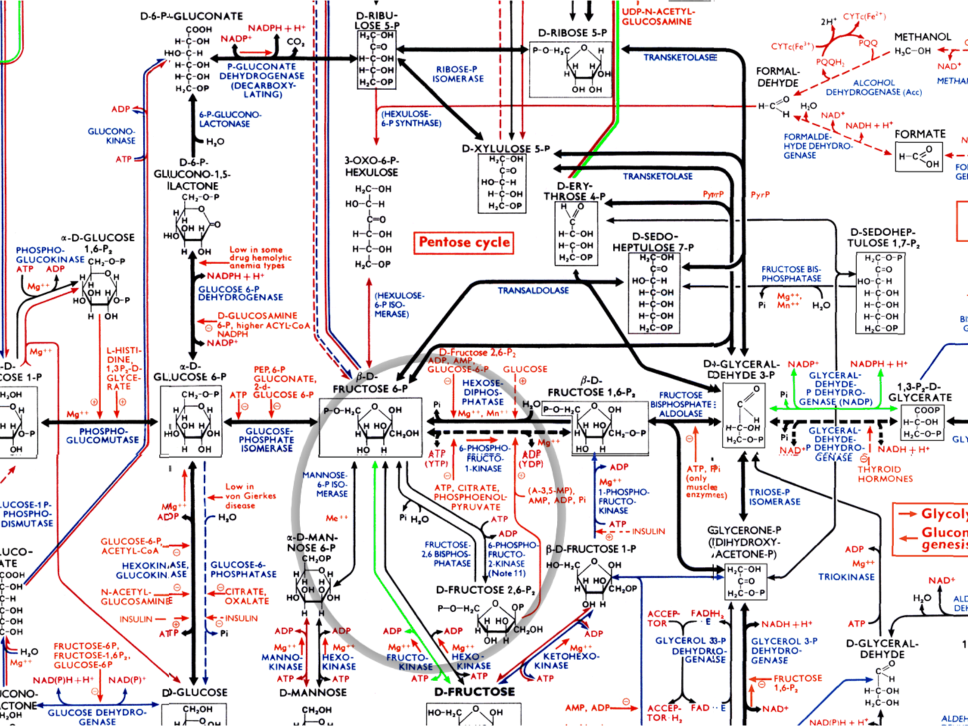
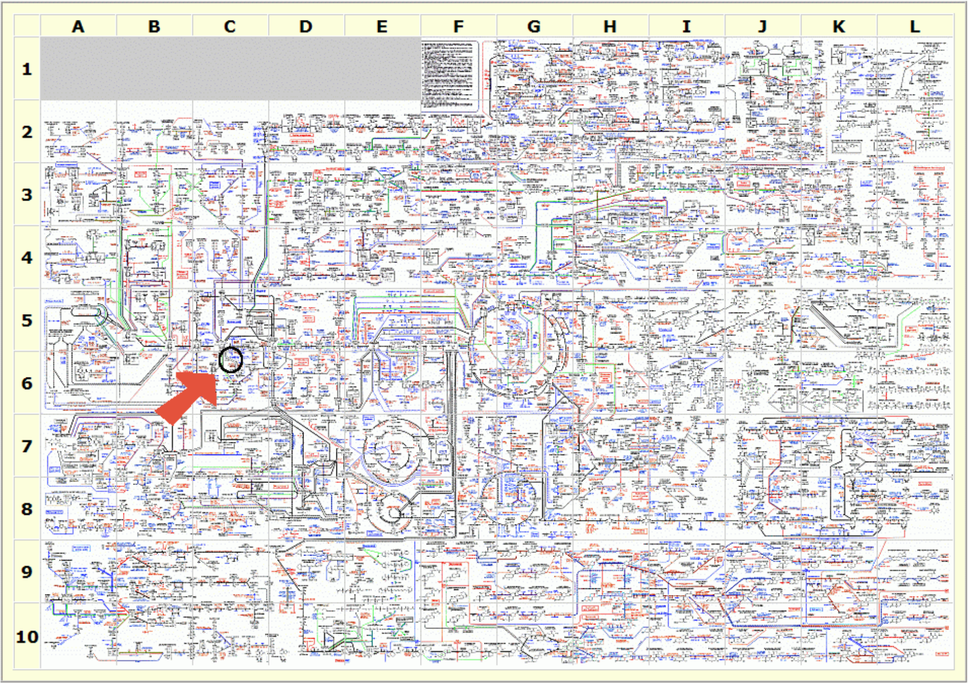




D-Fructose 2,6-P2
ADP, AMP,
GLUCOSE-6-P
β-D-
FRUCTOSE 6-P
HEXOSE-
DIPHOS-
PHATASE
Pi
Mg++, Mn++
H2O
ATP
(YTP)
6-PHOSPHO-
FRUCTO-
1-KINASE
Mg++
ADP
(YDP)
ATP, CITRATE,
PHOSPHOENOL-
PYRUVATE
(A-3,5-MP),
AMP, ADP,
MANNOSE-
6-P ISO-
MERASE
Me++
Pi H2O
ATP
ADP
FRUCTOSE-
2,6 BISPHOS-
PHATASE
6-PHOSPHO-
FRUCTO-
2-KINASE
(Note 11)
D-FRUCTOSE 2,6-P2
HO-H2
ADP
ADP
ADP
Mg++
Mg++
FRUCTO-
KINASE
HEXO-
KINASE
ATP


D-6-P-GLUCONATE
NADPH + H+
NADP+
CO2
P-GLUCONATE DEHYDROGENASE (DECARBOXYLATING)
D-RIBULOSE 5-P
D-RIBOSE 5-P
UDP-N-ACETYL-GLUCOSAMINE
TRANSKETOLASE
RIBOSE-P ISOMERASE
METHANOL
CYTc(Fe2+)
CYTc(Fe3+)
PQQ
PQQH2
FORMALDEHYDE
ALCOHOL DEHYDROGENASE (Acc)
NAD+
FORMATE
NADH + H+
FORMALDEHYDE DEHYDROGENASE
ADP
GLUCONOKINASE
ATP
6-P-GLUCONOLACTONASE
H2O
D-6-P-GLUCONO-1,5-LACTONE
(HEXULOSE-6-P SYNTHASE)
3-OXO-6-P-HEXULOSE
D-XYLULOSE 5-P
TRANSKETOLASE
D-ERYTHROSE 4-P
PyrP
Pentose cycle
D-SEDOHEPTULOSE 7-P
D-SEDOHEPTULOSE 1,7-P2
FRUCTOSE BISPHOSPHATASE
Mg++, Mn++
Pi
TRANSALDOLASE
α-D-GLUCOSE 1,6-P2
PHOSPHOGLUCOKINASE
Low in some drug hemolytic anemia types
NADPH + H+
GLUCOSE 6-P DEHYDROGENASE
D-GLUCOSAMINE 6-P, higher ACYL-CoA NADPH
NADP+
(HEXULOSE-6-P ISOMERASE)
Mg++
L-HISTIDINE, 1,3P2-D-GLYCERATE
α-D-GLUCOSE 1-P
α-D-GLUCOSE 6-P
PEP, 6-P GLUCONATE, 2-d-GLUCOSE 6-P
β-D-FRUCTOSE 6-P
D-Fructose 2,6-P2
ADP, AMP, GLUCOSE-6-P
GLUCOSE
HEXOSE-DIPHOSPHATASE
Mg++, Mn++
β-D-FRUCTOSE 1,6-P2
FRUCTOSE BISPHOSPHATE ALDOLASE
D-GLYCERALDEHYDE 3-P
NADP+
NADPH + H+
GLYCERALDEHYDE-P DEHYDROGENASE (NADP)
1,3-P2-D-GLYCERATE
PHOSPHOGLUCOMUTASE
GLUCOSE-PHOSPHATE ISOMERASE
6-PHOSPHOFRUCTO-1-KINASE
ATP (YTP)
ADP (YDP)
GLYCERALDEHYDE-P DEHYDROGENASE
NAD+
THYROID HORMONES
GLUCOSE-1P-PHOSPHODISMUTASE
Low in von Gierkes disease
MANNOSE-6-P ISOMERASE
ATP, CITRATE, PHOSPHOENOLPYRUVATE
(A-3,5-MP), AMP, ADP, Pi
ATP, Pi (only muscle enzymes)
1-PHOSPHOFRUCTOKINASE
INSULIN
TRIOSE-P ISOMERASE
GLYCERONE-P (DIHYDROXYACETONE-P)
Glycolysis
Gluconeogenesis
GLUCOSE-6-P, ACETYL-CoA
HEXOKINASE, GLUCOKINASE
GLUCOSE-6-PHOSPHATASE
N-ACETYL-GLUCOSAMINE
CITRATE, OXALATE
α-D-MANNOSE 6-P
FRUCTOSE-2,6 BISPHOSPHATASE
6-PHOSPHOFRUCTO-2-KINASE (Note 11)
D-FRUCTOSE 2,6-P2
β-D-FRUCTOSE 1-P
TRIOKINASE
FRUCTOSE-6P, FRUCTOSE-1,6P2, GLUCOSE-6P
NAD(P)H + H+
NAD(P)+
GLUCOSE DEHYDROGENASE
D-GLUCOSE
MANNOKINASE
HEXOKINASE
D-MANNOSE
FRUCTOKINASE
D-FRUCTOSE
KETOHEXOKINASE
ACCEPTOR
FADH2
GLYCEROL 3-P DEHYDROGENASE
NADH + H+
GLYCEROL 3-P DEHYDROGENASE
FRUCTOSE 1,6-P2
D-GLYCERALDEHYDE
AMP, ADP
ACCEPTOR H2
FAD
NAD+


A B C D E F G H I J K L
1 2 3 4 5 6 7 8 9 10

What can Computer Science do for Systems Biology?

Machines

Large Databases: Semistructured data; data integration; data mining

Large Simulations: Experiments *in silico*; parameter scans; folding search

Ideas

Language: Abstraction; modularity; semantics; formal models

Reasoning: Logics; behavioural description; model checking

Scope of Study

Processes

- Metabolic networks
- Regulatory systems: promotion, inhibition
- Signalling pathways
- Gene expression: translation, transcription

Models

- Discrete time, continuous time
- Discrete space, continuous space
- Deterministic, nondeterministic, probabilistic
- Qualitative, quantitative

Biochemical Simulation

Biologists routinely use one of two alternative approaches to computational modelling of biochemical systems:

- Stochastic simulation
  - Discrete behaviour: tracking individual molecules
  - Randomized: Gillespie's algorithm
- Ordinary Differential Equations
  - Continuous behaviour: chemical concentrations
  - Deterministic: Numerical ODE solutions

The classical approach is to use the mathematics directly as the target formal system. However, experience in Computer Science suggests the value of an intermediate *language* to describe a system. An expression in this language can then be analysed as it stands, or further mapped into (one or more) mathematical representations.

Topics to Cover

This course explores a variety of mathematical models for biological processes, and introduces formally precise languages to describe and reason about them.

- Petri Nets: Dynamic system behaviour; analysis of network properties.
- Temporal Logics: Linear time and branching time; model checking.
- Markov Systems: Probabilistic behaviour in continuous time.
- Stochastic Simulation: Gillespie algorithm; reaction kinetics.
- Qualitative vs. Quantitative Analyses: Differential equations.
- Biological Process Algebras: Modularity and compositional reasoning.

Useful Information

Timing

4.10pm Mondays and Thursdays through weeks 1–10 of Semester 2

Books

- D. J. Wilkinson.
  Stochastic Modelling for Systems Biology.
  Chapman & Hall/CRC, April 2006.
- M. Huth and M. Ryan.
  Logic in Computer Science: Modelling and Reasoning about Systems.
  Cambridge University Press, 2nd Edition, August 2004.

See course web page for further reading recommendations.

Communication

Web

http://www.inf.ed.ac.uk/teaching/courses/mlcsb/

The course web page carries lecture slides, a lecture log and links to resources mentioned, as well as occasional news and advice.

Lecturer

mailto:Ian.Stark@ed.ac.uk

The most effective way to contact the lecturer is by personal email, from your University email address.

Petri Nets

A *Petri Net* comprises some static components:

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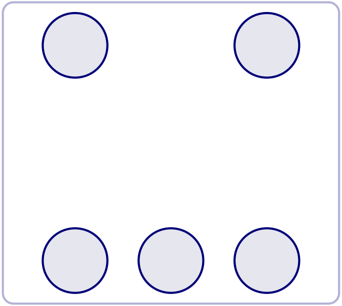
Places: Shown as circles;

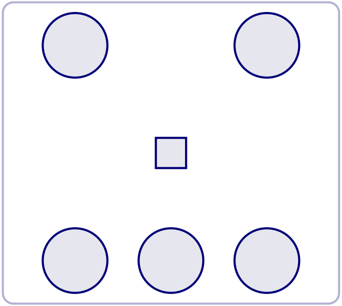


Petri Nets

A *Petri Net* comprises some static components:

Places: Shown as circles;

Transitions: Shown as squares;



Petri Nets

A *Petri Net* comprises some static components:

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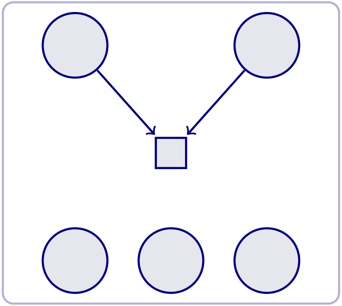
Transitions: Shown as squares;

Input arcs: From places to transitions;



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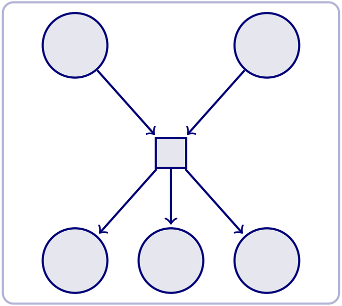
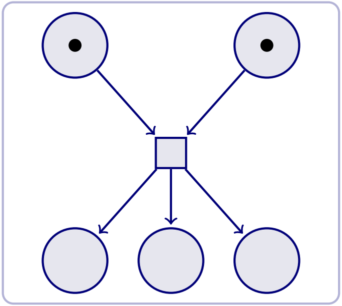
- Input arcs: From places to transitions;
- Output arcs: From transitions to places;



Petri Nets

A *Petri Net* comprises some static components:

Places: Shown as circles;
Transitions: Shown as squares;
Input arcs: From places to transitions;
Output arcs: From transitions to places;
Tokens: Sited at certain places;

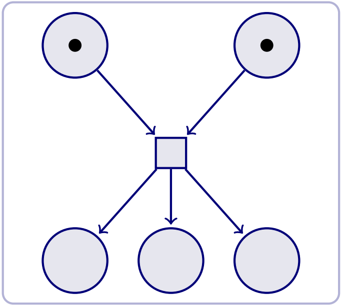


Petri Nets

A *Petri Net* comprises some static components:

Places:	Shown as circles;
Transitions:	Shown as squares;
Input arcs:	From places to transitions;
Output arcs:	From transitions to places;
Tokens:	Sited at certain places;

and a single dynamic action:



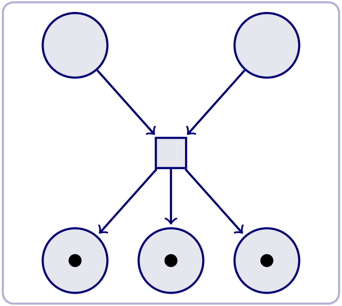
Petri Nets

A *Petri Net* comprises some static components:

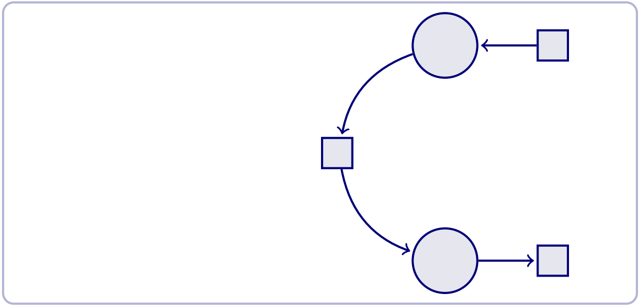
- Places: Shown as circles;
- Transitions: Shown as squares;
- Input arcs: From places to transitions;
- Output arcs: From transitions to places;
- Tokens: Sited at certain places;

and a single dynamic action:

Firing: When tokens move from input to output places.



Networks of Transitions



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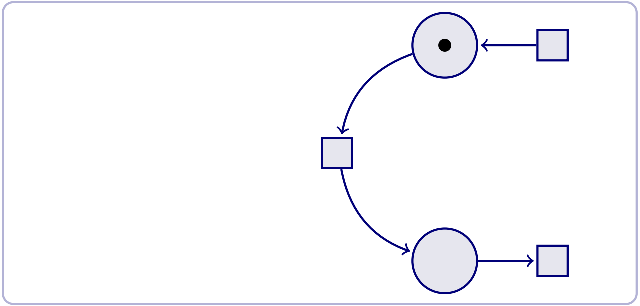

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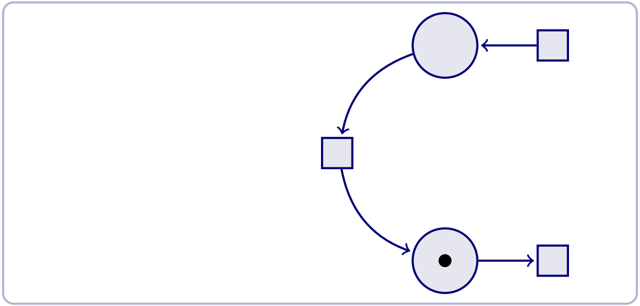

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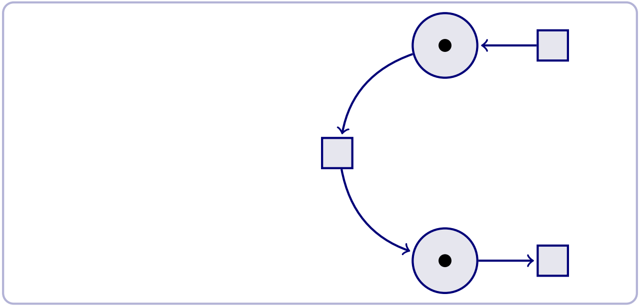

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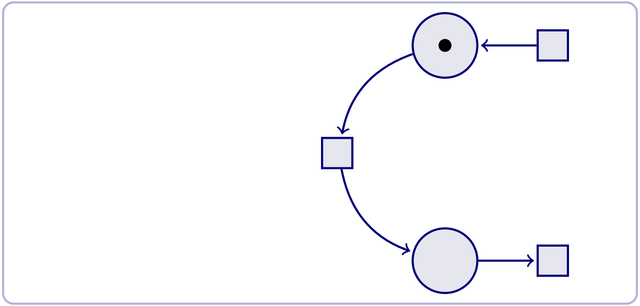

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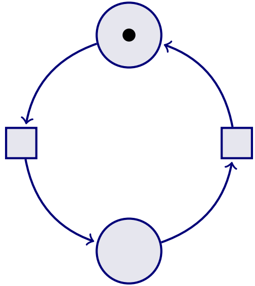

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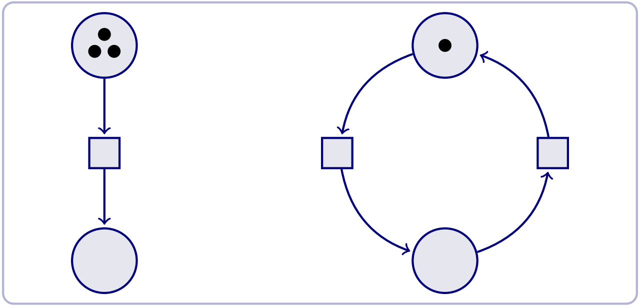

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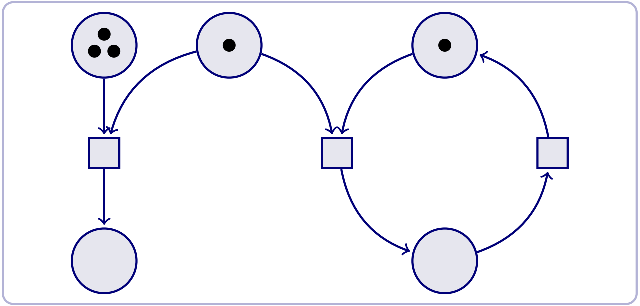
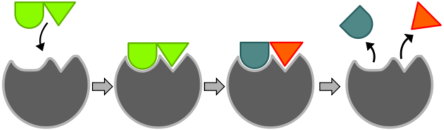


Example: Enzyme Catalysis



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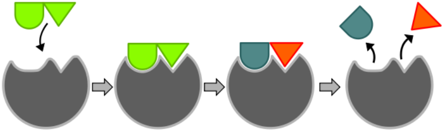

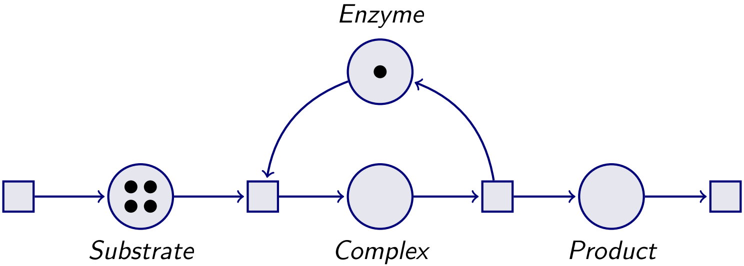

Homework

In preparation for the next lecture:

- Get a copy of the following paper.

  M. Heiner, D. Gilbert, and R. Donaldson.
  Petri Nets for systems and synthetic biology.
  In *Formal Methods for Computational Systems Biology*, Lecture Notes in Computer Science 5016. Springer-Verlag, 2008.

- Read Section 3 and Section 4.1, up to Figure 6.
- Look at some of the demonstrations on the Petri Net Pathways:

  http://genome.ib.sci.yamaguchi-u.ac.jp/~pnp/