Signal Processing Graduate Seminar IV: Stochastic Modelling for Systems Biology

Representations of biochemical networks

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October 27, 2008

Coupled chemical reactions

- a flexible way of specifying a quantitative model is to write down coupled chemical reactions corresponding to a model
  - need to have rate laws for every reaction: quantify the "probability" of a certain reaction to happen
  - initial amounts of all chemical species
- chemical reaction lists are difficult to "understand," whereas qualitative descriptions are not sufficiently detailed

Graphical representations, graphs

- displaying a model graphically helps in understanding, see Figure 2.1
- contains the same information as reaction list
- loops in the graph
- can be difficult to distinguish reactants and products
- can be formalized using directed graphs $\mathcal{G} = (V, E)$ where $V = \{1, \ldots, n\}$ and $E = \{(v_i, v_j) | v_i, v_j \in V, v_i \rightarrow v_j\}$, see Figure 2.2
- each node represents either a chemical species or a reaction and arcs specify a reaction pathway

Graphical representations (2)

[Figure 2.1]

Graphical representations (3)

[Figure 2.2]

Graphs

- a graph is *simple* if there are no (v_i, v_i) edges and there no repeated edges
- a simple graph is *bipartite* if nodes can be partitioned into two distinct subsets V_1 and V_2 and there are no connections within the same subset
- in a *weighted* graph each edge is associated with a numerical value
- coupled chemical reactions can be represented with weighted bipartite graphs
  - nodes are partitioned into chemical species and reactions
  - edges from species set to a reaction node specify the reactants
  - edges from a reaction node to species set specify the products
  - weights specify the stoichiometric coefficients
- the above specification of reaction graphs is closely related to Petri nets

Petri nets

- Perti nets are a mathematical framework to systems modeling together with an associated graphical representation
- Petri net corresponding to Figure 2.1 is shown in Figure 2.3
  - rectangular boxes represent reactions
  - edges in and out of boxes correspond to reactants and products
  - weights on edges specify the stoichiometries

Petri nets (2)

[Figure 2.3]

Petri nets (3)

- each species node (place) is associated with an integer count (token)
  - number of molecules, see Figure 2.4
- collection of tokens is a marking (state of the biological reaction system)
- Petri net shows what happens when transitions take place:
- example: repression binding and translation, see Figure 2.5
- old and new markings (states), see Table on page 23
- reaction can only take place if sufficiently many input reactants are available

Petri nets (4)

[Figure 2.4]

Petri nets (5)

[Figure 2.5]

Petri nets (6)

[Table on page 23]

Matrix formalism

- formal definition

[Formal definition from the book]

- structure of *Pre* and *Post* ensure that the underlying graph is bipartite
- a reaction t_i can take place only if $M_j \geq Pre_{ij}$ for all j

Matrix formalism (2)

- a concrete Petri net example corresponding to Figure 2.1 is shown in Table 2.1

[Table 2.1]

Matrix formalism (3)

- the same as Table 2.1 in mathematical terms

[Model definition from the book]

Matrix formalism (4)

- the molecular counts decrease and increase according to *Pre* and *Post*, respectively
- reaction matrix: difference $A = Post - Pre$
  - rows represent the effect of individual reactions
- stoichiometry matrix $S = A'$
- given an initial state M and transitions vector r the new state M^* is

$$M^* = M + Sr$$

Conservation law

- **Definition:** P-invariant is a non-zero vector y $(\in \mathbb{R}^u)$ that is a solution to the matrix equation $Ay = 0$
- P-invariant define the conservation laws of the network
- e.g. in the previous example $y = (1, 1, 0, 0, 0)^T$ is a P-invariant
- if y is a P-invariant then the linear combination of states, $y'M$, is conserved

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

Conservation law (2)

- **Definition:** T-invariant is a non-zero vector y ($\in \mathbb{Z}^{\nu}$) that is a solution to the matrix equation $Sx = 0$
- correspond to sequence of transitions that return to the initial state (recall: $M^* = M + Sr$)
- deterministic vs. stochastic models — non-integer vs. integer-valued
- e.g. reversible reactions
- T-invariance is trivial to verify but less straightforward to find (SVD)

Reachability

- **Definition:** a state M^* is reachable from state M if there exists a finite set of sequence of reactions so that $M^* = M + Sr$
- note that existence of solution to $M^* = M + Sr$ does not guarantee reachability