Signal Processing Graduate Seminar IV (SGN-9406): Stochastic Modelling for Systems Biology

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Course book

- Darren J. Wilkinson
  Stochastic Modelling for Systems Biology
  Chapman & Hall/CRC, 2006.
- today:
  - Section 1: Introduction

Modeling

- purposes of modeling
  - mathematical representation of the current state of knowledge: elements and interactions
  - test current knowledge: consistency with experimental data
    - learn model parameters/structure from data
  - use model predictively: virtual experiments
  - integrate sub-models into a larger model: interactions
- modeling important in biology
  - integrating knowledge and experimental data
  - testable predictions
  - make inference about biological phenomena

Stochastic modeling

- biological systems are typically considered as deterministic systems
- dynamics of biological systems (at detailed level) are intrinsically stochastic in nature

An example model

- linear birth-death process for bacterium
  - reproduces at rate λ
  - dies at rate μ
  - initial amount x_0
- continuous deterministic model

$$\frac{dX(t)}{dt} = (\lambda - \mu)X(t)$$

  has the solution

$$X(t) = x_0 \exp((\lambda - \mu)t)$$

- $\lambda - \mu$ is sufficient: population size will increase if $\lambda > \mu$, decrease if $\lambda < \mu$, remain the same if $\lambda = \mu$

An example model (2)

[Figure 1.1]

An example model (3)

- identifiability: experimental data only give information about $\lambda - \mu$
- cannot infer from experimental data if we have pure birth or pure death model
- problems: bacteria vary in number
  - discretely
  - stochastically
- see Fig. 1.2
- e.g. confidence intervals at time $t = 2$
- deterministic model never reaches level 0

An example model (4)

[Figure 1.2]

An example model (5)

- stochastic model depends on both λ and μ (see Fig. 1.3)
- stochastic rate constants cannot in general be estimated using a deterministic model
- similar observations apply to genetic and biochemical network models

An example model (6)

[Figure 1.3]

Chemical reactions

- a biological system can be represented in a number of ways: verbal, diagrams, graphs, ODEs, PDEs, **coupled chemical reactions**
- chemical reactions can be simulated and define full dynamic model
- chemical reactions with stoichiometric coefficients

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

- which chemical species react, in which proportions, and what is produced

A concrete example: protein dimerisation

- protein dimerisation

$$2P \longrightarrow P_2$$

- dissociation

$$P_2 \longrightarrow 2P$$

- reversible reaction can happen in both directions

$$2P \rightleftharpoons P_2$$

Motivation

- Stochastic modeling is particularly important for genetic and biochemical networks
- transcription is a central biological process

$\rightsquigarrow$ transcriptional regulation is important

Prokaryotic transcription

[Figure 1.4]

Prokaryotic transcription (2)

- gene g, promoter p, transcript r, RNA polymerase RNAP (see Fig. 1.4)

$$\begin{aligned} p + \mathrm{RNAP} &\rightarrow p \cdot \mathrm{RNAP} \\ p \cdot \mathrm{RNAP} &\rightarrow p + \mathrm{RNAP} + r \end{aligned}$$

- reactions do not necessarily form a closed system
- linear chain of reactions can sometimes be summarized as

$$p + \mathrm{RNAP} \rightarrow p + \mathrm{RNAP} + r$$

Prokaryotic transcription (3)

- transcription including elongation

$$\begin{aligned} p + \mathrm{RNAP} &\rightarrow p \cdot \mathrm{RNAP} \\ p \cdot \mathrm{RNAP} &\rightarrow p \cdot \mathrm{RNAP} \cdot r_1 \\ p \cdot \mathrm{RNAP} \cdot r_1 &\rightarrow p \cdot \mathrm{RNAP} \cdot r_2 \\ \vdots &\rightarrow \vdots \\ p \cdot \mathrm{RNAP} \cdot r_{n-1} &\rightarrow p \cdot \mathrm{RNAP} \cdot r_n \\ p \cdot \mathrm{RNAP} \cdot r_n &\rightarrow p + \mathrm{RNAP} + r \end{aligned}$$

- gene is blocked...

Eukaryotic transcription

[Figure 1.5]

Eukaryotic transcription (2)

- eukaryotic transcription is much more complex: see Fig. 1.5 for a simple model with transcription factors TF_1 and TF_2

$$
\begin{aligned}
g + \mathrm{TF}_1 &\rightleftharpoons g \cdot \mathrm{TF}_1 \\
g \cdot \mathrm{TF}_1 + \mathrm{TF}_2 &\rightleftharpoons g \cdot \mathrm{TF}_1 \cdot \mathrm{TF}_2 \\
g \cdot \mathrm{TF}_1 \cdot \mathrm{TF}_2 + \mathrm{RNAP} &\rightleftharpoons g \cdot \mathrm{TF}_1 \cdot \mathrm{TF}_2 \cdot \mathrm{RNAP} \\
g \cdot \mathrm{TF}_1 \cdot \mathrm{TF}_2 \cdot \mathrm{RNAP} &\longrightarrow g \cdot \mathrm{TF}_1 \cdot \mathrm{TF}_2 + \mathrm{RNAP} + r
\end{aligned}
$$

Prokaryotic transcription repression

- transcriptional regulation necessarily involves feedback (a definition for biological network)
- an example of repression: see Fig. 1.6

$$\begin{aligned} g + R &\rightleftharpoons g \cdot R \\ g + \mathrm{RNAP} &\rightleftharpoons g \cdot \mathrm{RNAP} \\ g \cdot \mathrm{RNAP} &\rightarrow g + \mathrm{RNAP} + r \end{aligned}$$

- g and $g \cdot R$ are different chemical species

Prokaryotic transcription repression (2)

[Figure 1.6]

Translation

- simplified reactions to produce an unfolded protein P_u and folded protein P from an mRNA molecule with the help of ribosome Rib

$$
\begin{aligned}
r + \mathrm{Rib} &\rightleftharpoons r \cdot \mathrm{Rib} \\
r \cdot \mathrm{Rib} &\longrightarrow r + \mathrm{Rib} + P_u \\
P_u &\longrightarrow P
\end{aligned}
$$

mRNA degradation

- simply

$$r \longrightarrow \emptyset$$

or

$$\begin{aligned} r + \mathrm{RNase} &\rightleftharpoons r \cdot \mathrm{RNase} \\ r \cdot \mathrm{RNase} &\longrightarrow \mathrm{RNase} \end{aligned}$$

- similar reactions for protein degradation and mRNA transport

Prokaryotic auto-regulation

- combine the previous building blocks of simple reactions into a auto-regulatory model (see Fig. 1.7)

$$
\begin{aligned}
g + P_2 &\rightleftharpoons g \cdot P_2 \\
g &\longrightarrow g + r \\
r &\longrightarrow r + P \\
2P &\rightleftharpoons P_2 \\
r &\longrightarrow \emptyset \\
P &\longrightarrow \emptyset
\end{aligned}
$$

Prokaryotic auto-regulation (2)

[Figure 1.7]

Lac operon

[Figure 1.8]

Lac operon (2)

- see Fig. 1.8

$$
\begin{aligned}
i &\rightarrow i + r_I \\
r_I &\rightarrow r_I + I \\
I + \mathrm{Lactose} &\rightleftharpoons I \cdot \mathrm{Lactose} \\
I + o &\rightleftharpoons I \cdot o \\
o + \mathrm{RNAP} &\rightarrow o \cdot \mathrm{RNAP} \\
o \cdot \mathrm{RNAP} &\rightarrow o + \mathrm{RNAP} + r \\
r &\rightarrow r + A + Z + Y \\
\mathrm{Lactose} + Z &\rightarrow Z
\end{aligned}
$$

Birth-death model

- the linear birth-death model

$$
\begin{aligned}
x &\longrightarrow 2X \\
X &\longrightarrow \emptyset
\end{aligned}
$$