

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

- 1 Modeling
 - General
 - Example
- 2 Chemical reactions
 - Coupled chemical reactions
- 3 Modeling genetic and biochemical networks
 - Transcription

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)

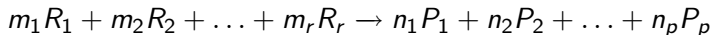
- stochastic model depends on both λ and μ (see Fig. 1.3)
- stochastic rate constants cannot in general be estimated using a deterministic model
- similar observations apply to genetic and biochemical network models

An example model (6)

[Figure 1.3]

Chemical reactions

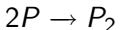
- a biological system can be represented in a number of ways: verbal, diagrams, graphs, ODEs, PDEs, **coupled chemical reactions**
- chemical reactions can be simulated and define full dynamic model
- chemical reactions with stoichiometric coefficients



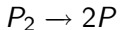
- which chemical species react, in which proportions, and what is produced

A concrete example: protein dimerisation

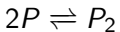
- protein dimerisation



- dissociation



- reversible reaction can happen in both directions



Motivation

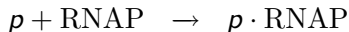
- Stochastic modeling is particularly important for genetic and biochemical networks
- transcription is a central biological process
- ~> transcriptional regulation is important

Prokaryotic transcription

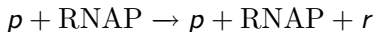
[Figure 1.4]

Prokaryotic transcription (2)

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

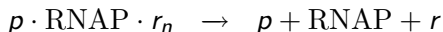
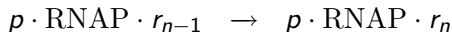
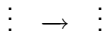
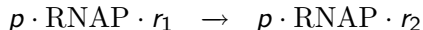
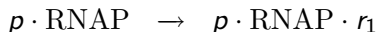
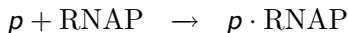


- reactions do not necessarily form a closed system
- linear chain of reactions can sometimes be summarized as



Prokaryotic transcription (3)

- transcription including elongation



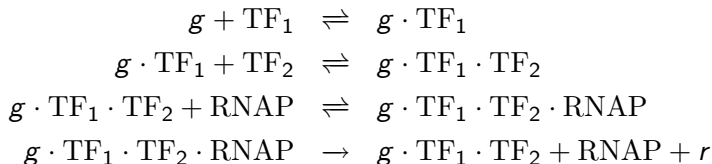
- gene is blocked. . .

Eukaryotic transcription

[Figure 1.5]

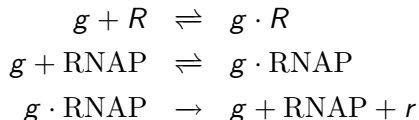
Eukaryotic transcription (2)

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



Prokaryotic transcription repression

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



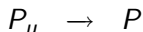
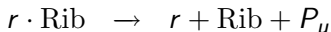
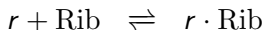
- g and $g \cdot R$ are different chemical species

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

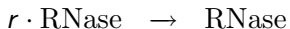
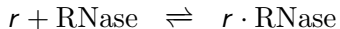


mRNA degradation

- simply



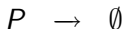
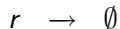
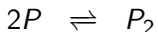
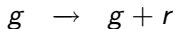
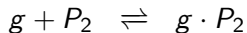
or



- 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)



Prokaryotic auto-regulation (2)

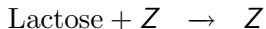
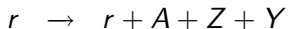
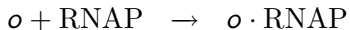
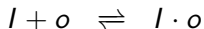
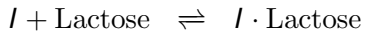
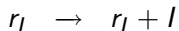
[Figure 1.7]

Lac operon

[Figure 1.8]

Lac operon (2)

- see Fig. 1.8



Birth-death model

- the linear birth-death model

