T-61.5110 Modeling biological networks

Exam, November 7th, 2009

You are NOT allowed to use calculators or any other additional equipments/material in the exam. Please write your answers in English. Please write carefully so that I can read your writing.

1. Consider the prokaryotic auto-regulation model in Figure 1, which is taken from the course book: g=gene, r=transcript, P=protein, $P2$=protein dimer (formed of two proteins P), $RNAP$=RNA polymerase, p=binding/operator site of $RNAP$, q=binding/operator site of P2; RNAP can transcribe the gene g unless $P2$ blocks the transcription. Construct the corresponding coupled chemical reactions (i.e., reaction network model). Also formulate the model as a Petri net $(P, T, Pre, Post, M)$. (6 points)

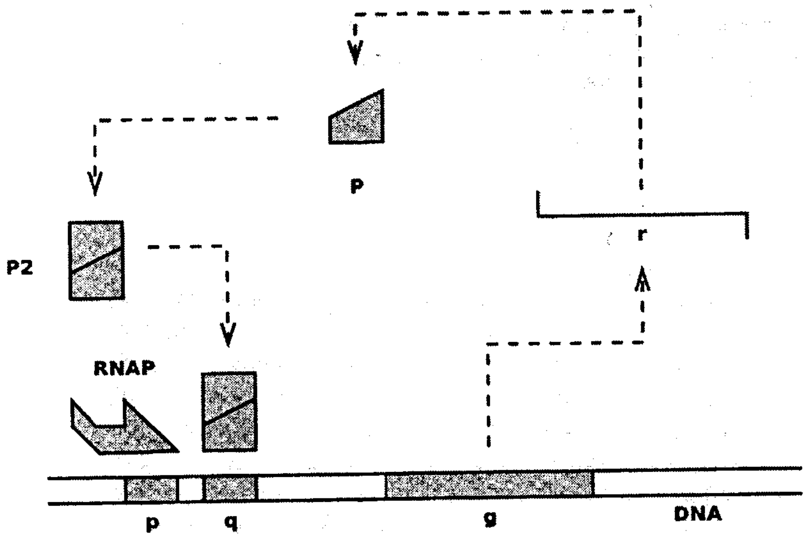

Figure 1: A simplified prokaryotic auto-regulation model.

2. Explain the Gillespie algorithm for simulating coupled chemical reactions. You can assume general rate constants $c_1, \ldots, c_v$ and hazard functions $h_1(\mathbf{x}, c_1), \ldots, h_v(\mathbf{x}, c_v)$ for all reactions. In addition to the simulation algorithm itself, briefly explain the connection to the theory of continuous-time Markov processes. (6 points)

3. a) Consider mass-action kinetics and a second-order reaction $R_i: \ X_j + X_k \rightarrow X_l$. Explain how the reaction hazard $h_i(\mathbf{x}, c_i)$ for the ith reaction R_i is computed. In addition, explain how the reaction hazard is computed for a third-order reaction $R_i: \ X_j + X_k + X_l \rightarrow X_m$. (3 points)

b) Explain the steepest descent method for (frequentist) parameter estimation in the context of ODE models, given time-series measurements. (3 points)

4. Explain the principles of Bayesian model selection (including the marginal likelihood) and how the Bayesian approach can be applied for choosing an optimal ODE network model structure, given time-series measurements of all variables. (6 points)

5. Consider the following (Michaelis-Menten) ODE system

$$\begin{aligned} d[S]/dt &= k_2[SE] - k_1[S][E] \\ d[E]/dt &= (k_2 + k_3)[SE] - k_1[S][E] \\ d[SE]/dt &= k_1[S][E] - (k_2 + k_3)[SE] \\ d[P]/dt &= k_3[SE] \end{aligned}$$

Use conservation laws to reduce the dimension of the system. Also explain why dimensionality reduction for ODEs is useful in general. (6 points)