Stochasticity in system biology
- a few examples -

Q1: Simulating stochastic systems. Gillespie algorithm

Consider a dynamical system made of Q reactions involving N species \( A(1), ..., A(N) \) such that the \( i \)th reaction \( R_i \) reads

\[
R_i : \sum_{j=1}^{N} c(j, i)A(j) \rightarrow \sum_{j=1}^{N} p(j, i)A(j)
\]

where \( c \) and \( p \) are stoichiometric coefficients for reactants and products, and \( k_i \) is the reaction rate constant. \( A_0 \) and \( t_{end} \) correspond respectively to the initial configuration of the system, and to the simulation time horizon. The temporal evolution of the system can be simulated thanks to the Gillespie algorithm. It consists of repeating (i) the selection of the time of the next reaction and (ii) the selection of the next reaction that occurs, until \( t_{end} \) is reached or no reaction is possible.

Denoting \( \alpha_i \) the propensities of reaction \( R_i \) and \( \alpha_0 \) their sum, justify that the probability density function \( P(\tau) \) of the next reaction occurrence time is \( \alpha_0 e^{-\alpha_0 \tau} \), and justify that this reaction is reaction \( R_J \) with probability \( \frac{\alpha_J}{\alpha_0} \). How could you sample the time \( \tau \) and the index \( J \) of the next reaction using these distributions? Implement the Gillespie algorithm. More precisely, write a function named \texttt{gillespiessa} that given \( c \), \( p \), \( k \), \( A_0 \) and \( t_{end} \), simulates one possible behavior of the stochastic system, called realization. The result will be given by a pair \( t, A \) describing event times and system state, respectively.

A1: Showing that the probability density function \( P(\tau) \) of the next reaction occurrence time is \( \alpha_0 e^{-\alpha_0 \tau} \) amounts to show that the probability that the next reaction fires during the time interval \([t+\tau, t+\tau+dt]\) equals \( \alpha_0 e^{-\alpha_0 \tau} dt \). This probability is the product of the probability that no reaction occurred during \([t, t+\tau]\) with the probability that some reaction occurred during \([t+\tau, t+\tau+dt]\). Let’s call P1 and P2 these two probabilities. The propensity of reaction \( R_i \) being \( \alpha_i \) means that this reaction occurs during a time interval \( dt \) with a probability \( \alpha_i dt \). One can then show that the occurrence of a reaction during a time interval \( dt \) has a probability \( \alpha_0 dt \). This is P2. To compute the property that no reaction occurred during \([t, t+\tau]\), we divide \( \tau \) in \( n \) equal intervals and find that the probability that nothing happened in any of the small time intervals is \((1- \alpha_0 \tau/n)^n\), which tends to \( e^{-\alpha_0 \tau} \) when \( n \) tends to infinity. Hence, the probability that the next reaction fires during the time interval \([t+\tau, t+\tau+dt]\) equals \( \alpha_0 e^{-\alpha_0 \tau} dt \). Among reactions, chances to fire are proportional to propensities. Hence, the reaction that fires is reaction \( R_i \) with probability \( \alpha_i / \alpha_0 \).

Using \( \tau = -\ln(r1)/\alpha_0 \), with \( r1 \) a standard uniform random number, gives \( \tau \) values following the distribution given above. Similarly, choosing the smallest integer \( J \) such that \( \sum_{i=1..J}(\alpha_i / \alpha_0) > r2 \), with \( r2 \) defined as \( r1 \), gives correctly-distributed reaction indices.
Q2: Analysis of a birth-and-death process

Consider the birth-and-death process in which a single species is produced at a rate \( \mu A \) and degraded at a rate \( \gamma A \). How can you represent this system using chemical reactions? What are the values of \( Q \), \( N \), \( k \), \( c \) and \( p \)? Define a function called `birth_and_death` taking as arguments \( c \), \( p \), \( k \), \( A_0 \), \( t_{end} \), and \( N_{real} \). Simulate the system behavior with initially 50 molecules, \( \mu=3 \), and \( \gamma=4 \), for 6 time units. Plot 50 realizations. Compute and plot the behavior of the corresponding deterministic system (i.e., using reaction rate equations). Compute and plot the mean and standard deviation of the realizations over time. Compute the extinction times and plot the corresponding histogram. Plot this information in the following three cases:

1) values for \( \mu \) and \( \gamma \) are (0,1), (3,4), or (10,11). \( A_0 \) equals 50.
2) values for \( \mu \) and \( \gamma \) are (3,4), or (4,4), or (5,4). \( A_0 \) equals 50.
3) values for \( \mu \) and \( \gamma \) are (3,4) and \( A_0 \) equals 5, 50 and 500.

In all cases, compare deterministic and stochastic behaviors, extinction times, asymptotic behaviors, and computational times.

References.
