

## Stochastic simulation of elementary chemical reactions

### Classroom problems

**Problem 1.** (Generating exponentially distributed random variables).

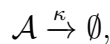
Let  $U \sim \mathcal{U}(0, 1)$ ,  $\lambda > 0$ , and let  $g : (0, 1] \rightarrow \mathbb{R}$  be

$$g(y) = -\frac{\ln(y)}{\lambda} = \frac{\ln(1/y)}{\lambda}.$$

Draw  $10^5$  realizations of  $g(U)$  when  $\lambda = 10$ . Next, plot a normalized histogram of your realizations together with the evaluation of the probability density function of an exponential distribution with parameter  $\lambda$ .

*Hint:* When  $X \sim \text{Exp}(\lambda)$ , we can use Julia's function `pdf(Exp(1/λ), x)` from package `Distributions.jl`. It is enough to plot it for  $x \in [0, 1]$ .

**Problem 2.** (Gillespie Algorithm - naive formulation). Consider the chemical reaction



where  $\mathcal{A}$  is the chemical species of interest and  $\kappa$  is the rate constant of the reaction. Obtain an evolution of  $(N_{\mathcal{A}}(t))_{t \geq 0}$  for the first 30 seconds by stochastic simulation, given the following parameter values

$$\begin{aligned}\kappa &= 0.1 \text{sec}^{-1} \\ N_{\mathcal{A}}(0) &= n_{\mathcal{A}}(0) \\ &= 20 \\ \Delta t &= 0.001 \text{sec}.\end{aligned}$$

Step 1. Compute the propensity function  $\nu(t) = n_{\mathcal{A}}(t)\kappa\Delta t$ .

Step 2- Generate a random number  $u$  uniformly distributed in the interval  $[0, 1]$ .

Step 2. Update the number of molecules if  $u < n_{\mathcal{A}}(t_k)\kappa\Delta t$ . Continue with step 1 until stopping time  $T$  or other stopping criteria.

**Problem 3.** (Gillespie Algorithm).

Step 1. Compute the propensity function  $\nu_{n_r}(t)$  for each of the  $N_r$  reactions. Then compute

$$\alpha = \sum_{n_r}^{N_r} \nu_{n_r}(t).$$

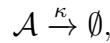
Step 2. Compute the time when the next chemical reaction takes place as  $t + \tau$ , where  $\tau$  is sampled from the exponential distribution with parameter  $\alpha$  (Problem 1).

Step 3. Find out which reaction occurs at time  $t + \tau$ , that is, find  $j$  such that

$$u \geq \frac{1}{\alpha} \sum_{n_r=1}^{j-1} \nu_{n_r}(t) \quad \text{and} \quad u < \frac{1}{\alpha} \sum_{n_r=1}^j \nu_{n_r}(t), \quad u \sim \mathcal{U}(0, 1),$$

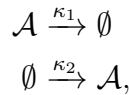
or sample  $j$  from the multinomial distribution with probability vector  $\alpha^{-1}[\nu_1(t), \nu_2(t) \dots, \nu_{N_r}(t)]$ . Then the  $j$ th reaction takes place. Update numbers of reactants and products of the  $j$ th reaction. Continue with step 1 for time  $t + \tau$ .

(a) (Stochastic Simulation of Degradation) consider again the chemical reaction



where  $\mathcal{A}$  is the chemical species of interest and  $\kappa$  is the rate constant of the reaction. Draw 10 realizations of  $(N_{\mathcal{A}}(t))_{t \geq 0}$  for the first 100 seconds using the Gillespie algorithm above. Consider  $n_{\mathcal{A}}(0) = 20$  as the initial condition on the number of molecules and  $\kappa = 0.1 \text{sec}^{-1}$  as the rate of the reaction. Plot a time-series of your realizations.

(b) (Stochastic Simulation of Production and Degradation) consider now the chemical reactions



where  $\mathcal{A}$  is the chemical species of interest and  $\kappa_1, \kappa_2$  are the rate constants of the reactions. Draw 10 realizations of  $(N_{\mathcal{A}}(t))_{t \geq 0}$  for the first 30 seconds. Consider  $n_{\mathcal{A}}(0) = 0$  as the initial condition on the number of molecules,  $\kappa_1 = 0.1 \text{sec}^{-1}$  and  $\kappa_2 = 1 \times 10^3 \text{sec}^{-1} \text{m}^{-3}$  as the reaction rates, and  $V = 10^{-3} \text{m}^3$  as the volume of the vessel where the reactions take place. Plot a time-series of your realizations, as well as the evolution of the stochastic mean  $M(t)$  given by

$$M(t) = \frac{\kappa_2 V}{\kappa_1} + \left( M(0) - \frac{\kappa_2 V}{\kappa_1} \right) \exp(-\kappa_1 t).$$

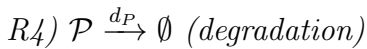
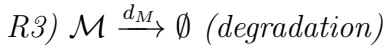
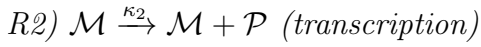
Hint: reactions of the type  $\emptyset \xrightarrow{\kappa} \mathcal{A}$  have propensity function of the form  $\nu(t) = \kappa V$ .

(c) draw  $10^6$  realizations of the setup in (b) during the first 100 seconds of the reaction and plot a normalized histogram of your realizations at the stopping time  $T = 100 \text{sec}$ . Compare the histogram with the solution to the steady-state version of the chemical master equation,  $\phi(\cdot)$ , given by

$$\begin{aligned} \phi(0) &= 1, \\ \phi(1) &= \frac{\kappa_2 V}{\kappa_1} \phi(0), \\ \phi(n+1) &= \frac{1}{\kappa_1(n+1)} [\kappa_1 n \phi(n) + \kappa_2 V \phi(n) - \kappa_2 V \phi(n-1)], \quad \text{for } n \geq 1. \end{aligned}$$

# Homework

**Problem 4.** Consider a model of transcription and translation consisting of three species ( $\mathcal{G}, \mathcal{M}, \mathcal{P}$ ), representing Gene, mRNA, and Protein, respectively. We suppose that there are four possible transitions in our model:



Consider a volume  $V$  of size one and assume that we always have one Gene, that is  $N_{\mathcal{G}}(t) \equiv 1, t \geq 0$ . With the choice of rate constants  $\kappa_1 = 200$ ,  $\kappa_2 = 10$ ,  $d_M = 25$ , and  $d_P = 1$ , and of initial quantities  $n_{\mathcal{M}}(0) = 50$  and  $n_{\mathcal{P}}(0) = 8$ :

(a) draw a realization of the stochastic model up to time  $t = 8$ .

(b) allow for the possibility that the protein dimerizes via the reaction  $2\mathcal{P} \xrightarrow{\kappa_3} \mathcal{D}$ , and that the degradation of the dimer is allowed by the reaction  $\mathcal{D} \xrightarrow{d_d} \emptyset$ . With the new set of species ( $\mathcal{G}, \mathcal{M}, \mathcal{P}, \mathcal{D}$ ), draw a realization of the stochastic model when  $\kappa_3 = 0.01$ ,  $d_d = 1$  and  $n_{\mathcal{D}}(0) = 0$ . Hint: reactions of the type  $2\mathcal{A} \xrightarrow{\kappa} \mathcal{B}$  have propensity function of the form  $\nu(t) = \frac{\kappa}{V^2} N_{\mathcal{A}}(t)(N_{\mathcal{A}}(t) - 1)$ .