Simulationstechnik A
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Exercise 2 - Gillespie's Algorithm and τ-Leaping

For all our exercises, we will consider the following system consisting of substrate S_1, enzyme S_2, complex S_3 and product S_4:

$$S_1 + S_2 \xrightarrow{c_1} S_3$$
$$S_3 \xrightarrow{c_2} S_1 + S_2$$
$$S_3 \xrightarrow{c_3} S_4 + S_2$$

It is often referred to as Michaelis Menten Kinetics and will serve as a manageable system to train techniques and algorithms from the lecture.

1. **Random variables used in Gillespie's Stochastic Simulation Algorithm**

   Gillespie's Stochastic Simulation Algorithm relies on two important random variables. The first determines the type of reaction happening next while the second one specifies the duration of that reaction. Suppose there is access to a uniformly distributed random variable $\mathcal{U}(0,1)$ that returns values between 0 and 1. Find a transformation for $\mathcal{U}(0,1)$ to obtain the following random variables:

   a) A random variable $\mathcal{I}$ that returns the index for the next reaction where the probability $\mathcal{P}$ of reaction r happening is proportional to its propensity $a_r(X(t))$. The corresponding probability density is therefore given by

   $$\mathcal{P}_{\mathcal{I}}(\mathcal{I} = j) = \frac{a_j(X(t))}{\sum_{i=1}^{3} a_i(X(t))} \qquad j \in \{1,2,3\} \tag{1}$$

   b) An exponentially distributed random variable $\mathcal{E}(\lambda)$ with $\lambda = \sum_{i=1}^{3} a_i(X(t))$. The probability density of $\mathcal{E}$ is then given by

   $$\mathcal{P}_{\mathcal{E}}(\mathcal{E} = t) = \lambda e^{-\lambda t} \qquad t \in \mathbb{R}_+ \tag{2}$$

   Hint: If a transformation in closed form is not possible, you can also provide an algorithm returning the solution.

2. **A closer look at τ-Leaping**

   While Gillespie's Stochastic Simulation Algorithm approximates the solution of the underlying CME with arbitrary high precision (given enough sample paths), τ-Leaping uses an approximation preventing it from providing the exact solution.

   a) Which condition needs to be fulfilled in order to keep the resulting error as small as possible?

   b) What kind of distribution is used in τ-Leaping to determine how often a certain reaction j is triggered during the next time interval $[t, t + \tau]$?

3. **Implementing Gillespie's Stochastic Simulation Algorithm**

   a) In comparison to the CME in exercise 1, what kind of boundary treatment is needed? Implement your solution.

   b) Define the two random numbers ξ_1 and ξ_2 needed in every step of Gillespies's Algorithm according to (1) and (2).

   c) Implement the condition under which each of the 3 possible reactions is triggered.

   d) Describe the qualitative difference of results obtained using CME and Gillespie's Algorithm, respectively. Therefore also vary the number of traces.

4. **Implementing τ-Leaping**

   a) Define the numbers of triggered reactions for each reaction type.

   b) What kind of boundary treatment is needed? Implement your solution.

   c) What happens if the number of time steps is reduced to very low numbers?