Chapter 14
Stochastic Approach for Enzyme Reaction in Nano Size via Different Algorithms

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Abstract Stochastic simulations have been done for enzyme kinetics reaction with Michaelis-Menten mechanism in low population number. Gillespie and Poisson algorithms have been used for investigation of population number and fluctuation population around their mean values as a function of time. Our result shows that equilibrium time for population dynamics via Poisson algorithm is smaller than Gillespie algorithm. Variations of average population number versus time for all species have the following order: deterministic approach (mean fields) $>$ Gillespie $>$ Poisson. There is asymptotic limit for fluctuation population as a function of time via Poisson algorithm but there is not such trend for fluctuation population via Gillespie algorithm. There is a maximum for fluctuation population for all species for kinetics reaction with Michaelis-Menten mechanism as a function of time via Gillespie algorithm. The stochastic approach has also been used for horse liver alcohol dehydrogenase which catalyses the NAD^+ (nicotinamide heterocyclic ring) oxidation of ethanol to acetaldehyde and three kinds of third order reactions. Probability distribution function and fluctuation population for reactants are calculated as a function of time. Increasing a variety of species for third order reactions leads to decrease of coefficient variation.

14.1 Introduction

Within its host cell, a complex coupling of transcription, translation, genome replication, assembly, and virus release processes determines the growth rate of a virus. Mathematical models that account for these processes can provide insights into the understanding as to how the overall growth cycle depends on its constituent

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reactions [1]. A virus infection may be initiated by a single virus particle that delivers its genome, a single molecule of DNA or RNA, to its host cell [2]. Under such conditions, the inherently stochastic nature of the ensuing processes may give rise to dynamics that differ significantly from those predicted by deterministic models. At the molecular level, random fluctuations are inevitable, with their effect being most significant when molecules are at low numbers in the biochemical system. This typically occurs in the regulation of gene expression where transcription factors interact with DNA binding sites in the gene's regulatory sequences. These intrinsic fluctuations have recently been measured using fluorescent probes [3, 4]. Deterministic approach for studying the kinetics of small systems is not appropriate [5]. To investigate the chemical kinetics, the stochastic approach is more consistent than deterministic approach for small systems [6–9]. Deterministic approach does not give any information regarding the fluctuation of concentration as a function of time [10–12]. McQuarrie et al. [10, 11] worked on the irreversible first and second order elementary reactions and compared the average concentration obtained from the master equation (ME) with that of the deterministic approach. In addition, Rose and Zheng [12] solved numerically the cubic Schlogl model with a single steady state. Erdi and Toth [13] also considered simple enzyme kinetics, ligand migration kinetics and membrane noise, to compare the stochastic results with those of deterministic. Stochastic simulations of homogeneous chemically reacting systems have been done by Fabio and Stefano [14] for Lotka–Volterra mechanism. Kramers theory of the rates of chemical reaction was reviewed by Gomes [15]. Many studies have been done on enzyme kinetics reaction with Michaelis-Menten mechanism [16–18].

The stochastic version of the enzyme kinetics predicts that catastrophic bottlenecks in the system are more likely than one would expect from deterministic theory for Michaelis-Menten mechanism [17]. Many biochemical reactions occurring in human are catalyzed by enzymes. On the other hand all biological reactions occur in low population number. Stochastic simulation yields a correct average population number for all reactants species as a function of time. There is no information regarding fluctuation via deterministic approach. In present work development of stochastic simulation for enzyme kinetics has been done via two different algorithms namely Gillespie and Poisson.

$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} E + P \tag{14.1}$$

Rate constants for k_1, k_2 and k_3 are 10 (molecule^{-1}.s^{-1}), 0.1 (s^{-1}) and 0.14 (s^{-1}) respectively. The mentioned rate constants can be applied for Chymotrypsin enzyme [19]. Fluctuation populations for all species in enzyme reaction have been calculated via the two mentioned algorithms. Many biological reactions contain some elementary reactions, therefore we investigate probability distribution, coefficient variation, average number of particles, and discrepancy for the number of particles with regard to the stochastic and deterministic approaches as a

function of time for reversible second order and three kinds of third order reaction namely:

$$A + B \underset{k_2}{\overset{k_1}{\rightleftarrows}} C + D \tag{14.2}$$

$$3\mathrm{A} \rightarrow \mathrm{P} \tag{14.3}$$

$$2\mathrm{A} + \mathrm{B} \rightarrow \mathrm{P} \tag{14.4}$$

$$\mathrm{A} + \mathrm{B} + \mathrm{C} \rightarrow \mathrm{P} \tag{14.5}$$

It is worthwhile to notice that McQuarrie et al. [10, 11] did mention that the master Eq. 14.2 can be solved exactly by using the method of separation of variables and the ordinary differential equation. However the evaluation of Fourier type coefficients is very difficult and it seems unlikely that numerical results could be easily found for the coefficients [20]. It is noteworthy that the master equation was exactly solved only at the equilibrium state by Darvey et al. [21].

14.2 Methodology

14.2.1 Master Equation for General Chemical Reaction

A Markov process, which satisfies the Markov property, is defined by the following relation:

$$P(y_n, t_n | y_{n-1}, t_{n-1}, \ldots y_1, t_1) = P(y_n, t_n | y_{n-1}, t_{n-1}) \tag{14.6}$$

where

$$t_1 < t_2 < \ldots < t_n \tag{14.7}$$

The Markov property merely expresses that, for a Markov process, the probability of a transition at time t_{n-1} from a y_{n-1} value to a y_n value at time t_n (Eq. 14.6) depends only on the value of y_{n-1} at time t_{n-1} and not to the previous history of the system [22]. For a discrete set of states, the ME may be given as [23]:

$$\frac{\mathrm{d}P_n(t)}{\mathrm{d}t} = \sum_j W_{j,n} P_j(t) - W_{n,j} P_n(t) \tag{14.8}$$

$W_{n,j}$ is the conditional probability that n reactant molecules exist in the system at time $t + \Delta t$, assuming that j reactant molecules existed at time t [23].

14.2.2 Stochastic Algorithm and Simulation

Another way to investigate the kinetics of a small system is stochastic algorithm. Up to now several authors have applied the stochastic algorithms [24–29]. In recent years, stochastic modeling has emerged as a physically more realistic alternative for modeling of the *vivo* reactions [2]. Let consider X as the time of the event. By a constant hazard we mean that:

$$P(X \in (t, t+dt] | X > t) = \alpha dt \tag{14.9}$$

where $\alpha > 0$ is a constant whose value may be calculated as, $\alpha = \sum_{i=1}^{M} W_{j,n} = \sum_{i=1}^{M} \alpha_i$, where $\alpha_i = W_{j,n} = k_i \frac{j!}{n!(j-n)!}$, k is a rate constant and it can be obtained via density functional approach [30, 31]. For a small δt we will have:

$$P(X \in (t, t+dt] | X > t) = \alpha \delta t \tag{14.10}$$

Considering a time $t > 0$, and a large integer N, dividing the interval $(0, t]$ into N subintervals of the form $((i-1)\delta t, i\delta t]$, i $= 1, 2, \ldots,$ N where $\delta t = \frac{t}{N}$, then we have:

$$P(X > t) = P[(X \notin (0, t])] = P(\{(X \notin (0, \delta t])\} \cap \{X \notin (\delta t, 2\delta t]\} \cap \ldots \{X \notin (N-1)\delta t, t]\}) \tag{14.11}$$

Hence

$$\begin{aligned} P(X > t) &= P(X \notin (0, \delta t]) P(X \notin (\delta t, 2\delta t] | X > \delta t) \\ &\quad \ldots P(X \notin ((N-1)\delta t, t] | X > (N-1)\delta t) \\ &\approx (1 - \alpha \delta t) \times (1 - \alpha \delta t) \times \ldots (1 - \alpha \delta t) \\ &= (1 - \alpha \delta t)^N \\ &= \left(1 - \frac{\alpha t}{N}\right)^N \end{aligned} \tag{14.12}$$

If $N \to \infty$ and $\delta t \to 0$, therefore Eq. 14.12 will convert to $\exp(-\alpha t)$ then $P(X \leq t) = (1 - \exp(-\alpha t))$. Consequently, whenever we consider a time dependent event with constant hazard α, in Gillespie algorithm [24–27], we can conclude that the time distribution is an exponential function. By choosing two uniform random numbers and within the interval $[0, 1]$ and by definition of two following expressions, we may write:

$$\tau = \frac{1}{\alpha} \ln\left(\frac{1}{r_1}\right) \tag{14.13}$$

$$\sum_{i=1}^{\mu-1} \alpha_i < r_2 \alpha \leq \sum_{i=1}^{\mu} \alpha_i \tag{14.14}$$

There are three loops for algorithm as follows:

1. Calculating $\alpha_i = k_i \frac{j!}{n!(j-n)!}$, whereas k is a rate constant ($1 \leq \mu \leq M$).
2. Generating two uniform random numbers r_1 and r_2 and calculating τ and μ according to Eqs. 14.13 and 14.14.
3. Increasing t by τ and adjusting population of reactants for reaction μ.

In Poisson algorithm, simulation time which is needed for the phenomenon to take place is [26, 31]:

$$\Pr(P(\lambda t = n)) = \frac{e^{-\lambda t}(\lambda t)^n}{n!} \tag{14.15}$$

and

$$\lambda t = \sum_i k_i \frac{j!}{n!(j-n)!} \tag{14.16}$$

where k_i, j, and n are rate constants, initial population, number of particles which are created or destroyed on the basis of stoichiometry coefficient of reaction i and $\lambda = \alpha$.

14.3 Results and Discussion

14.3.1 Stochastic Simulation for Average Number of Particles via Gillespie Algorithm for Michaelis-Menten Reaction

It is possible to study enzymatic reactions at the level of a single molecule via fluorescence correlation spectroscopy [32]. At low population of reactant, the usual description of such reactions via rate equations breaks down, so more appropriate stochastic models of single-molecule Michaelis-Menten kinetics have been developed recently [16, 32]. Stochastic simulations have been done for Eq. 14.1 for enzyme (E), substrate (S), intermediate (ES) and product (P) species. Stochastic simulation result has been shown for substrate via Gillespie algorithm in Fig. 14.1. Initial populations for substrate, enzyme, intermediate and product species are 100, 10, 0, and 0 respectively. It is worthwhile to notice that rate constant k_1, k_2 and k_3 of 10 (molecule^{-1}.s^{-1}), 0.1 (s^{-1}), 0.14 (s^{-1}) can explain a real dynamics of Chymotrypsin enzyme. On the basis of Fig. 14.1, substrate population decreases as a function of time and finally it approaches zero.

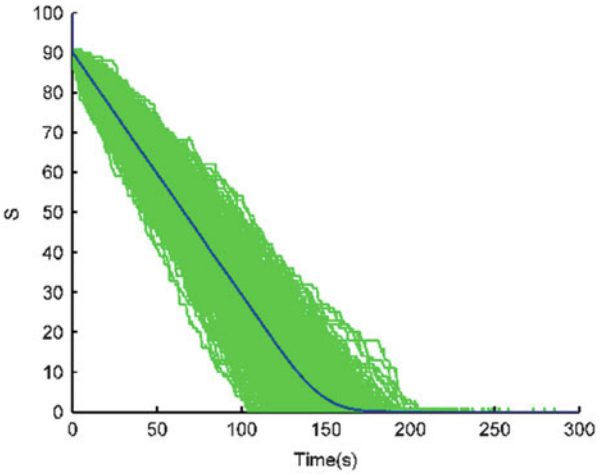


Fig. 14.1 1,000 stochastic simulations for population number of product (P) species and its average as a function of time via Gillespie algorithm

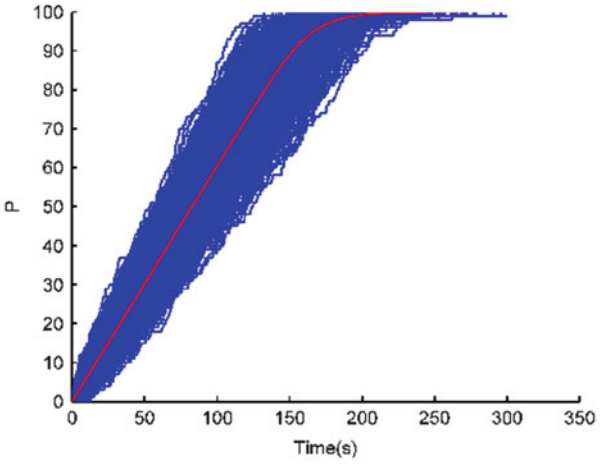


Fig. 14.2 Gillespie algorithm for 1,000 stochastic simulations of substrate population number and its average as a function of time

Figure 14.1 shows the average of 1,000 stochastic simulations via Gillespie algorithm for substrate species as a function of time.

Figure 14.1 indicates that fluctuation of substrate population is not small. On the basis of Eq. 14.1, 1,000 stochastic simulations have been done for product species (P). The result of stochastic simulation is shown in Fig. 14.2. On the basis of Fig. 14.2, product population increases as a function of time. It is important to notice that there is a fluctuation around mean population number of product species. The obtained simulation result is consistent with that observed in the literature [33].

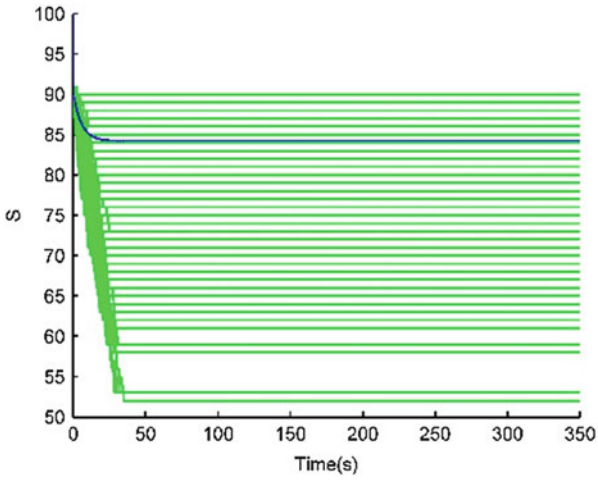


Fig. 14.3 1,000 stochastic simulations via Poisson algorithm for substrate population as a function of time

14.3.2 Poisson Algorithm for Stochastic Simulation

Stochastic simulations have been done for substrate species via Poisson algorithm. Similar to Gillespie algorithm, 1,000 stochastic simulations have been done for average population number of substrate species via Poisson algorithm. Result of Poisson algorithm for substrate species is shown in Fig. 14.3. Figure 14.3 indicates that substrate population approaches the equilibrium as a function of time quickly. Stationary population for substrate species via Poisson algorithm is 85 particles which is greater than zero particle for substrate species from Gillespie algorithm.

Stochastic simulation is investigated for population number of product species as a function of time. The result of simulation for product species is shown in Fig. 14.4. Average population number of product species from stochastic simulation via Poisson algorithm shows that stationary population for product species is 5 particles. On the basis of Fig. 14.4, average population number for product species is very much smaller than average population number of product from Gillespie algorithm. If 100 particles as an initial population for substrate are considered, the population of substrate species is predicted to be 100 particles in stationary state. As a result, Poisson algorithm does not predict the correct population number for stationary state of Michaelis-Menten kinetics. It is worthwhile to notice that equilibrium time for substrate and product species via Poisson algorithm is less than Gillespie algorithm. Variation of population for substrate and product as a function of time via Poisson algorithm is smaller than Gillespie algorithm (see Figs. 14.1, 14.2, 14.3, and 14.4).

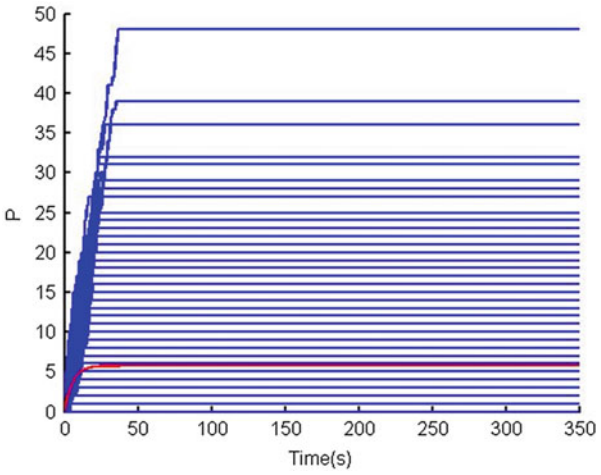


Fig. 14.4 1,000 stochastic simulations for population number and its average as a function of time for product species via Poisson algorithm

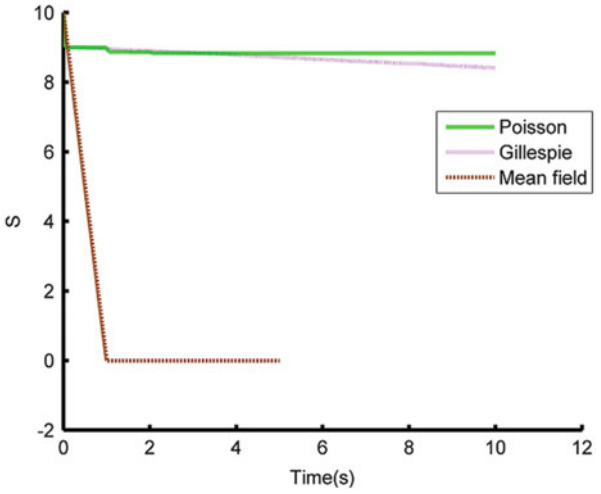


Fig. 14.5 Average population number for substrate species as a function of time via Gillespie, Poisson algorithms and mean field approach

14.3.3 Comparison of Gillespie and Poisson Algorithm with Mean Field Approach

Comparison of Gillespie and Poisson algorithms with mean field approach (deterministic differential equation) has been done for substrate population as a function of time. 1,000 stochastic simulations have been done to obtain average number of substrate. Initial population for substrate, enzyme, intermediate, and product of 10, 1, 0, 0 is taken respectively.

On the basis of Fig. 14.5, substrate population from mean field approach, stochastic simulations via Gillespie and Poisson algorithms are shown as a function

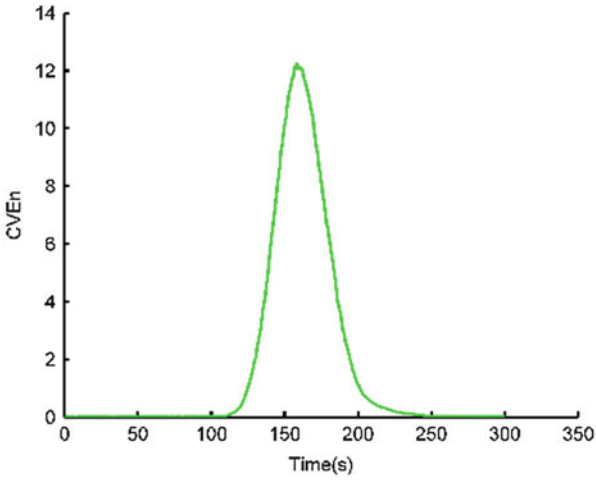


Fig. 14.6 Fluctuation population number as a function of time for enzyme (CVEn) from averaging of 1,000 simulations via Gillespie algorithm

of time. Population variation of substrate species via mean field approach is greater than Poisson and Gillespie algorithm. On the other hand, substrate population approaches equilibrium in lower time via mean field approach. There is a little variation for substrate population as a function of time via Poisson and Gillespie algorithms. As a result, equilibrium time for substrate population via Poisson and Gillespie is greater than mean field approach.

14.3.4 Fluctuation of Population for Substrate, Enzyme, Intermediate, Product Species as a Function of Time

Mean field approach does not represent fluctuation population $CV(t)$

$$CV(t) = < N^2(t) > - < N(t) >^2 \tag{14.17}$$

during the dynamics, where N(t) is number of particles. It is worthwhile to note that there is a significant fluctuation for the number of particles in low population level. Stochastic simulations have been done for investigation of fluctuation of population for all species in Michaelis-Menten reaction as a function of time via Poisson and Gillespie algorithms. Average result of 1,000 stochastic simulations for fluctuation population of enzyme (CVEn) and substrate (CVS) versus time have been shown in Figs. 14.6 and 14.7 via Gillespie algorithm respectively. Initial population for substrate, enzyme, intermediate, product of 100, 10, 0, 0 is considered respectively.

On the basis of Fig. 14.6, fluctuation population for enzyme species is zero initially and it increases after elapsing time, then it approaches zero finally. Result of stochastic simulation for fluctuation population number for intermediate (CVES), product (CVP) species are shown versus time in Figs. 14.8 and 14.9 respectively.

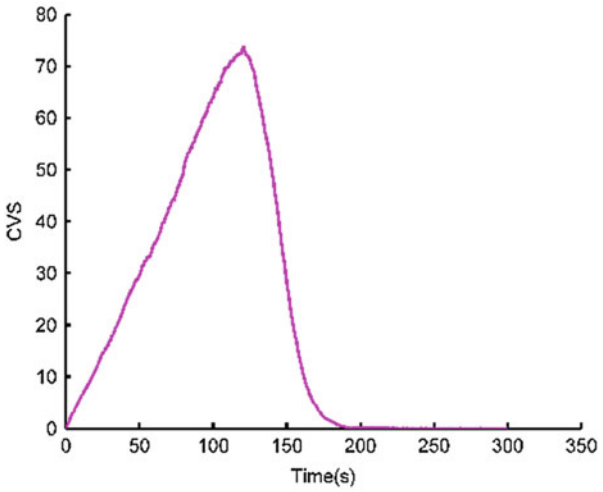


Fig. 14.7 Average of 1,000 stochastic simulations of substrate species (CVS) versus time via Gillespie algorithm

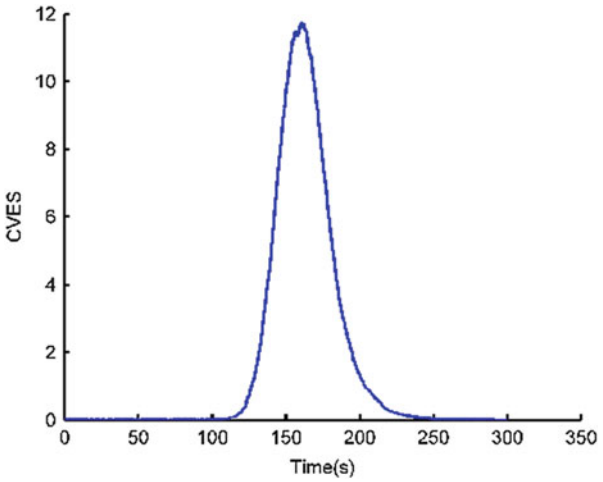


Fig. 14.8 Fluctuation population of intermediate species (CVES) as a function of time via Gillespie algorithm

14.3.5 Comparison of Gillespie and Poisson Fluctuation of Population

Gillespie and Poisson algorithms have been used for investigation of fluctuation population of product species as a function of time. Result of average of 1,000 stochastic simulations is shown in Fig. 14.10. It indicates fluctuation population for product species via Gillespie algorithm is greater than Poisson algorithm. Fluctuation population for product species approaches a constant value as a function of time. On the other hand fluctuation population for product species via Gillespie algorithm first increases, after some time it approaches its maximum value, then it decreases and approaches zero finally.

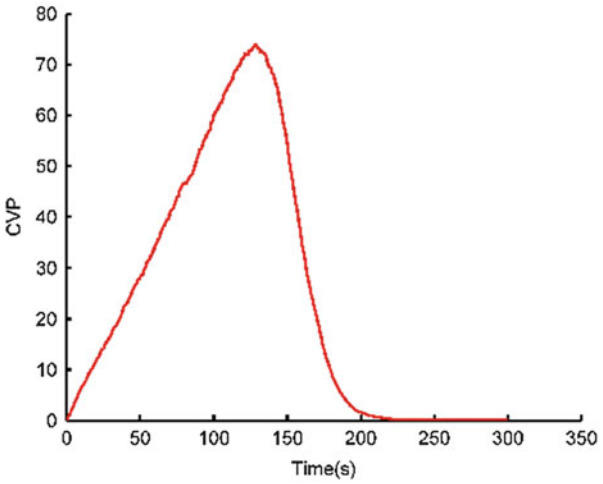


Fig. 14.9 Gillespie algorithm for fluctuation population of product species (CVP) as a function of time

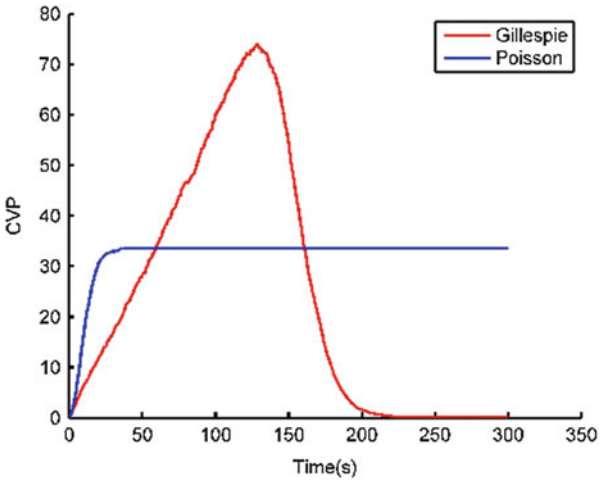


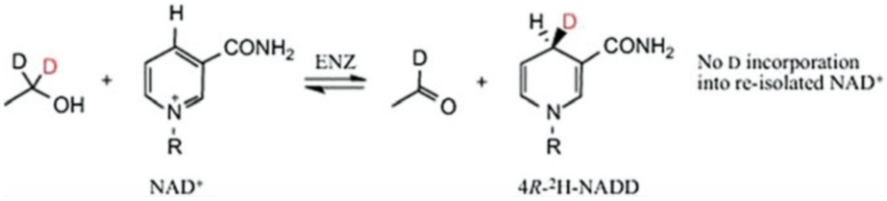
Fig. 14.10 Comparison of Gillespie and Poisson algorithms for fluctuation of product population as a function of time

14.3.6 Numerical Solution of Master Equation of Some Elementary Reactions

Master Equation for Second Order Reversible Reaction

An example of a second order reversible reaction is the horse liver alcohol dehydrogenase which catalyses the NAD^+ (nicotinamide heterocyclic ring) for oxidation of ethanol to acetaldehyde. Incubation of the enzyme with deuterated ethanol CH_3CD_2OH followed by re-isolation of oxidized NAD^+ revealed no deuterium

incorporation into the oxidized cofactor, showing that the deuterium atom transfer to the cofactor is stereospecific, which is removed in the reverse reaction [34].



(14.18)

In order to derive the master equation for the second order reversible reaction, Eq. 14.2, we suppose a, b, c and d, with their values achieved randomly, as the number of A, B, C, D species, respectively. The possible states of a system at time t which could lead to state specified by a, b, c, d at time $t + \Delta t$ are (a + *1*, b + *1*, *c-1*, *d-1*) and (a, b, c, d). Consequently, we may choose $\Delta t \to 0$. If the initial concentrations of A, B, C and D are a_0, b_0, c_0 and d_0, respectively at $t = 0$, then due to the fact that the total number of species is constant, we may get a conclusion as below:

$$a_0 - a = b_0 - b = c - c_0 = d - d_0 \tag{14.19}$$

Then

$$\begin{aligned}\frac{\mathrm{d}P_a(t)}{\mathrm{d}t} =& k_1(a+1)(b_0 - a_0 + a + 1)P_{a+1}(t) + k_2(c_0 + a_0 - a + 1)(d_0 + a_0 - a + 1)P_{a-1}(t) \\ &- [k_1 a(b_0 - a_0 + a) + k_2(c_0 + a_0 - a)(d_0 + a_0 - a)]P_a(t)\end{aligned} \tag{14.20}$$

This is the master equation for the reversible second order reaction. This equation has been already derived by McQuarrie without giving any solution for it [20]. Later, we will discuss its numerical solution.

Master Equation for Three Kinds of Third Order Reaction

The solution of deterministic reaction rate for Eq. 14.3 can be shown:

With a similar argument which led to Eq. 14.20, we may find the ME as:

$$\begin{aligned}\frac{\mathrm{d}P_x(t)}{\mathrm{d}t} =& \frac{1}{6}P_{x+3}(t) \times k \times (x+3) \times (x+2) \times (x+1) \\ &- \frac{1}{6}P_x(t) \times k \times (x) \times (x-1) \times (x-2)\end{aligned} \tag{14.21}$$

To obtain master equation Eq. 14.4, let concentrations of A and B at time t be $X(t)$ and $Y(t)$, respectively. We may define

$$Z_0 \equiv 2Y(t) - X(t) \tag{14.22}$$

According to both Eqs. 14.8 and 14.22 we can write:

$$\begin{aligned}\frac{dP_x(t)}{dt} =& \frac{1}{4}P_{x+2}(t) \times (x+2) \times (x+1) \times (x+Z_0+2) \\ &- \frac{1}{4}P_x(t) \times k \times (x) \times (x-1) \times (x+Z_0)\end{aligned} \tag{14.23}$$

In Eq. 14.23, coefficient $\frac{1}{4}$ is derived from Eq. 14.22 and combinational term.

To obtain master equation Eq. 14.5, let the concentrations of A, B and C be $x(t)$, $y(t)$, $z(t)$, respectively, at time t. We define the time independent variables Z_1 and Z_2 as:

$$Z_1 \equiv B(t) - A(t) \tag{14.24}$$

$$Z_2 \equiv C(t) - A(t) \tag{14.25}$$

With a similar discussion which led to Eq. 14.20 we find the master equation as:

$$\begin{aligned}\frac{dP_x(t)}{dt} =& P_{x+1}(t) \times k \times (x+1) \times (x+Z_1) \times (x+Z_2) \\ &- P_x(t) \times k \times (x) \times (x+Z_1) \times (x+Z_2)\end{aligned} \tag{14.26}$$

Numerical Solution of Master Equation

Number of particles given by deterministic approach, A_d, can be easily obtained from the solution of the rate equation (Note that A_d is the same as A). However, the average number of particles obtained from the solution of Master equation, $\langle A_m \rangle$, given by the stochastic approach may be easily calculated as:

$$A_m = \sum_A AP_A(t) \tag{14.27}$$

where $A(t)$ is the number of A and $P_A(t)$ is the probability of having A particles at time t. Consider the following equation:

$$\Delta A(t) = A_m - A_d \tag{14.28}$$

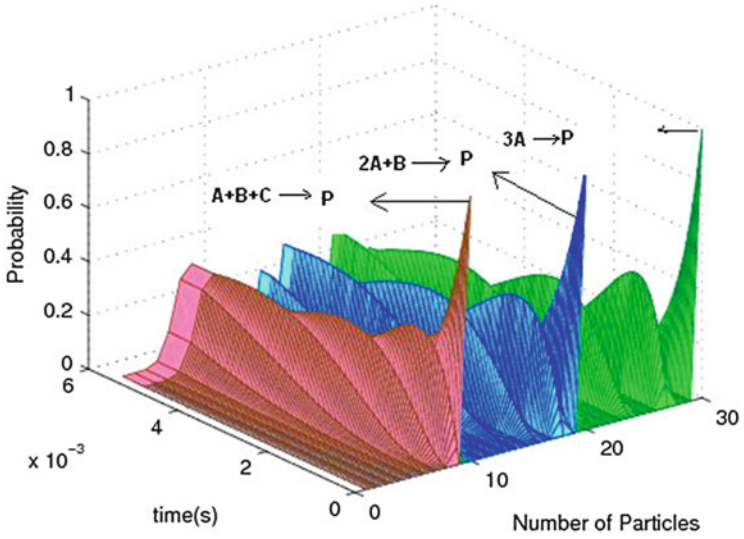


Fig. 14.11 Probability of having A molecules as a function of time and number of A particles for Eqs. 14.3, 14.4, and 14.5, when total number of molecules is 30

where A_m and A_d are the average number of A species obtained from the Master equation and deterministic approaches, respectively (Note that the probability distribution function for A in deterministic approach is a delta function). At $t = 0$ the initial conditions are:

$$P_A(0) = 1 \text{ if } A = A_0 \tag{14.29}$$

$$P_A(0) = 0 \text{ if } A \neq A_0 \tag{14.30}$$

$$\text{then } A_m = A_0 \text{ and}$$

$$\Delta A(0) = A_m - A_d = 0 \tag{14.31}$$

For numerical solution of Master equation, we have chosen the value of $dt = 0.00005$ s for each time step, for smaller time steps all quantities become unchanged. Besides that, we have calculated all values of $P_A(t)$ and then the average number of A molecules. Result of probability distribution of Eqs. 14.3, 14.4, and 14.5 is shown in Fig. 14.11, right to left, respectively. In the same way, the mean value of $\langle A^2 \rangle$ and $\langle A \rangle^2$ can be calculated, from which we may calculate the coefficient variation, CF, as follows:

$$CF = \frac{\langle A^2 \rangle - \langle A \rangle^2}{\langle A \rangle^2} \tag{14.32}$$

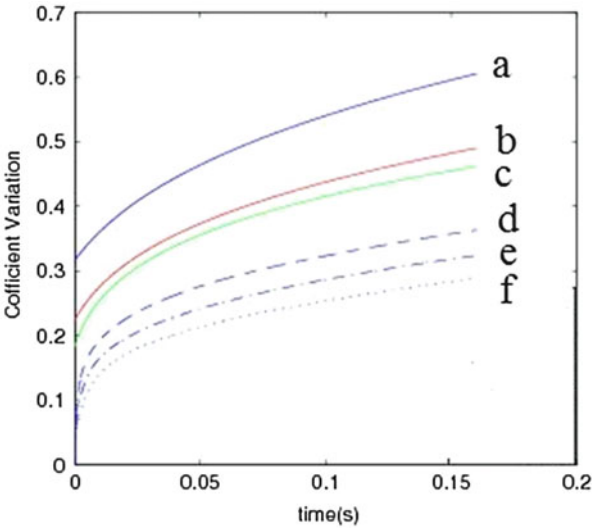


Fig. 14.12 The comparison of *CF* obtained from equilibrium statistical mechanics (*a, b, c*) and the Master equation (*d, e, f*) for three different third order reactions Eqs. 14.3, 14.4, and 14.5 respectively (Initial number of reactant in all of the reactions is 90 and $Z_1 = 0, Z_2 = 0$)

It is worthwhile to note that the value of CF versus time for three different types of third order reactions are shown in Fig. 14.12 and are compared to those obtained from equilibrium statistical mechanics $\frac{1}{\sqrt{A}}$. As shown in Fig. 14.12, the value of CF obtained from the solution of ME is smaller than $\frac{1}{\sqrt{A}}$ of the equilibrium statistical mechanics for all reactions. By using Markov assumption via the mentioned time step, the probability of having A molecules at time $t, P_A(t)$, may be calculated numerically. The results of such calculations for Eq. 14.2 are given in Fig. 14.13. Also the CF for the second order reversible reaction is calculated, for which the results are shown in Fig. 14.14.

14.4 Conclusions

We have simulated enzyme kinetics reaction via stochastic simulation. Two different algorithms namely Gillespie and Poisson have been used for stochastic simulation. Our results show that equilibrium time via Poisson algorithm is smaller than Gillespie algorithm. Fluctuation population via Poisson algorithm is lower than Gillespie algorithm as a function of time. There is an asymptotic limit for fluctuation population for product species as a function of time via Poisson algorithm. Fluctuation population via Gillespie algorithm is zero at the first time, and it increases as a function of time, then it approaches its maximum value. Finally it decreases and goes to zero. Average population number via Gillespie algorithm is less than Poisson algorithm. Also Master equations have been solved for three different third order reactions, namely Eqs. 14.3, 14.4, and 14.5, and for the reversible second order

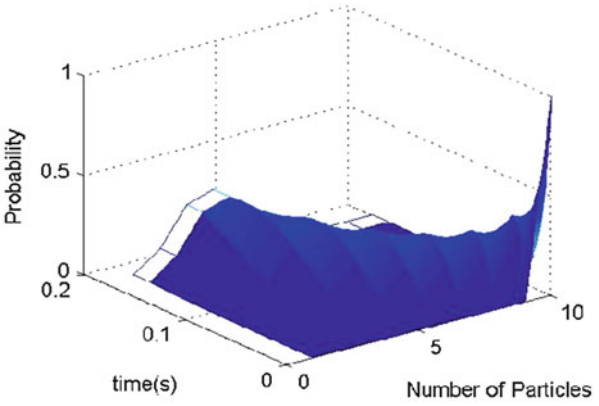


Fig. 14.13 Probability of having A molecules for Eq. 14.2 as a function of time and the number of A molecules

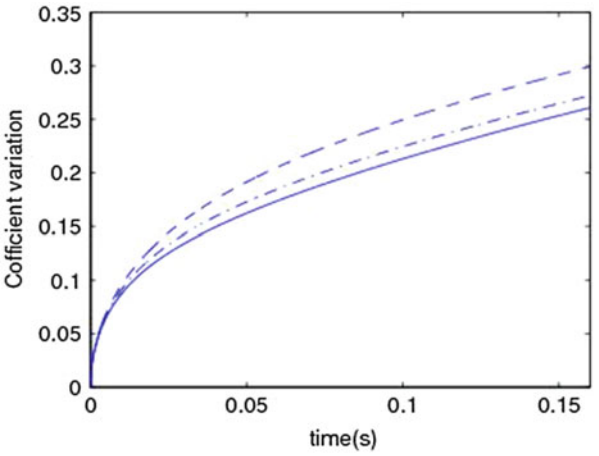


Fig. 14.14 Calculated coefficient variation for Eq. 14.2 when A = 10 (*dash* –), 20 (*dash dot* -.-.), 30 *solid* -) as a function of time

reaction Eq. 14.2. Graph of probability of particles and fluctuation about the mean value for third order and reversible second order reactions are shown in Figs. 14.11, 14.12, 14.13, and 14.14 respectively. For all third order reactions, fluctuation about the mean value is greater than those of the second order reactions (see Figs. 14.12 and 14.13). For elementary kinetics of small systems, maximum coefficient variance is smaller than $\frac{1}{\sqrt{N}}$ (Fig. 14.12) (N is number of particles). Besides that, by increasing a variety of species, coefficient variation decreases (see Fig. 14.12).

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