Two Examples of Deterministic versus Stochastic Modeling of Chemical Reactions

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There are two general methods to predict the time evolution of each species' concentration in chemical reactions. The first method involves analytical development, without using computers, of a rate law from a set of coupled differential equations that describes the time dependence of the concentrations. Approximations, such as the steady state approximation, are used to combine and simplify the set of differential equations. There is a severe limitation for this method—it is only applicable to relatively simple chemical processes. The second method involves numerical simulation using computers. Numerical simulation has been widely recognized as a powerful tool to complement lab experimentation and to enhance understanding of chemical reactions *(1–6)*.

Computer simulation methods can be based on a deterministic approach or on a stochastic (or probabilistic) approach. In the deterministic approach *(1–4),* a set of differential equations describing the time dependence of the concentrations is solved using analytical or numerical methods such as Euler or Runge–Kutta. It is assumed that the complete time behavior of the chemical system is contained in the solution of the set of equations. In other words, given an initial number of reactant molecules, it is assumed that the number of molecules that have reacted after a period of time, Δt, is fixed and dependent on the reaction rate constants.

The starting point in the stochastic approach is different from the deterministic approach—it is assumed that each reaction is a random event that can take place with a certain probability related to the thermodynamic properties of the reacting molecules. Thus, the evolution of the system over time is dependent on a series of consecutive probabilistic events. This implies that, given an initial number of molecules, there is not just one possible time evolution, but many, each with its probability and with all the probabilities adding up to one. These probabilities can be established by observing a sufficiently large number of such reactions; thus, the reactions follow a well-defined, probabilistic rate law.

There is a link between deterministic and stochastic modeling. The reaction rate constants of the deterministic modeling are interpreted in terms of probabilities in the stochastic approach and the differential reaction rate equations of deterministic modeling are nearly equivalent to the differential equation that describes the time evolution of the mean of the stochastic process.

Although the use of stochastic models is increasing in several fields of physical chemistry, such as polymer science, the deterministic approach is commonly used in articles concerning the teaching of chemical kinetics. The stochastic approach requires a larger mathematical foundation than the deterministic approach, particularly in probability theory. However, the intrinsic nature of chemical reactions is stochastic, as has been pointed out by de Levie *(7)*. Each reaction is a discrete event that takes place with a given probability. In addition, several authors *(6–9)* have pointed out that there are many chemical and biochemical processes where deterministic models are inaccurate.

In the deterministic approach it is assumed that each molecule behaves as an average molecule, but there are reactions where these assumptions do not hold. These reactions depend on the behavior of a very small number of participating molecules (sporadic events), such as some biological processes, explosions, and nucleation processes. All these reactions, of increasing importance in current chemistry, can only be accurately simulated and modelled using a stochastic approach *(8)*.

The two approaches are compared by examining two examples. Four MATLAB programs that implement both the deterministic and the stochastic modeling of the examples are presented. The first example is the following reaction:

$$ X \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B \tag{1} $$

It is assumed that $N_B(t)$, the number of molecules of B, is initially so large that at any time it is constant and is equal to N_B. Given N_B, k_1, k_2, and the initial number of molecules of X, $N_X(0)$, the program produces a graphical representation of both the deterministic and stochastic time evolution of the number of molecules of X, $N_X(t)$.

The second example is the set of Schlögl reactions *(10)*:

$$ A + 2X \underset{k_2}{\overset{k_1}{\rightleftharpoons}} 3X $$
$$ B \underset{k_4}{\overset{k_3}{\rightleftharpoons}} X \tag{2} $$
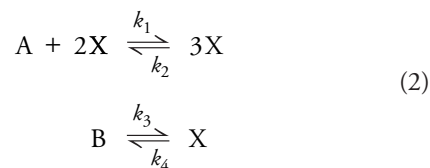
It is assumed that the initial number of molecules of A and B are so large that $N_A(t)$ and $N_B(t)$ can be considered constant over time and equal to N_A and N_B, respectively. This is a bistable process, which is more difficult to model than the first example. In a bistable process, $N_X(t)$ evolves towards either of two possible final state values, depending on the initial value and, in the stochastic approach, also on a random component. The modeling of this set of reactions is treated in detail by Gillespie *(10)*.

Although the results will be examined in detail in later sections, the graphs to illustrate how the stochastic and deterministic approaches differ are discussed here. The results obtained when the deterministic and stochastic approaches are applied to the first example, eq 1, are shown in Figure 1. In both curves $N_X(t)$ evolves towards the same unique final state value of 80. The only difference between the two curves is the fluctuations of the stochastic curve around the deterministic curve. Also note that while the deterministic curve is unique, the stochastic curve will change in each simulation. This idea will be explained further in the following pages.

The results obtained from the deterministic and stochastic simulations of the Schlögl process, eq 2, in two different runs starting with the same $N_X(0)$, are shown in Figures 2 and 3. In the two runs, the deterministic simulation evolves towards the same final state along the same curve (note the different x-axis scale). However, the stochastic simulation evolves towards a final state of 110 in the first run (Figure 2) and towards a final state of 450 in the second run (Figure 3). This illustrates the essential difference between the two approaches—two stochastic simulations of the same problem with the same initial values can evolve towards two different final states. In the following sections, we will discuss the theoretical models and how the results obtained in the stochastic simulation relate to the prediction of the deterministic model and to real-life experiments.

Theoretical Models

The deterministic and stochastic modeling of chemical reactions are compared by applying them to the first example, eq 1.

Deterministic Approach

In the deterministic approach, the rate of change of $N_X(t)$ (the number of molecules of X) as a function of time is given by eq 3:

$$\frac{dN_X(t)}{dt} = k_2 N_B - k_1 N_X(t) \qquad (3)$$

The final state values are then the zeros of the equation:

$$\frac{dN_X(t)}{dt} = 0$$

Stochastic Approach

In the stochastic approach, given an initial number of molecules of X, $N_X(0)$, there is not just one possible time evolution of the number of molecules of each species, but many evolutions or sample paths, each with its probability and with all probabilities adding up to one. The deterministic behavior is the average of all these possible stochastic evolutions. To illustrate the stochastic approach, consider time slices, dt, so small that either only one reaction or no reaction at all can occur in the interval $(t, t + dt)$. Let $N_X(t)$ and $N_X(t + dt)$ be random variables; these are the number of X molecules in the two time points. The difference between these two random variables, $dN_X(t) = N_X(t + dt) - N_X(t)$, is
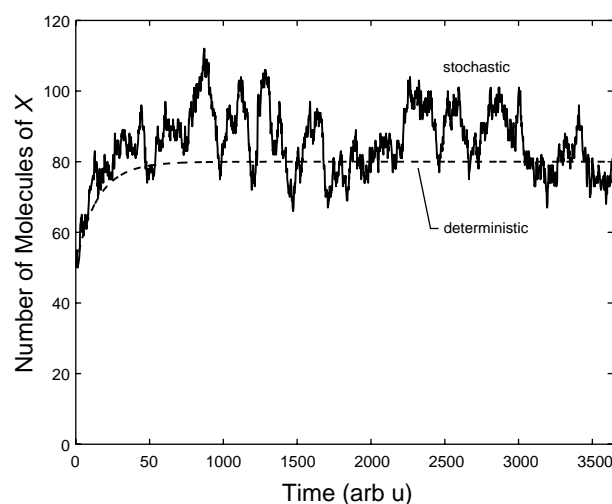

Figure 1. Simulation of the monostable process, eq 1: $N_X(0) = 50$, $N_B = 5000$, $k_1 = 0.01$, $k_2 = 1.6 \times 10^{-4}$.
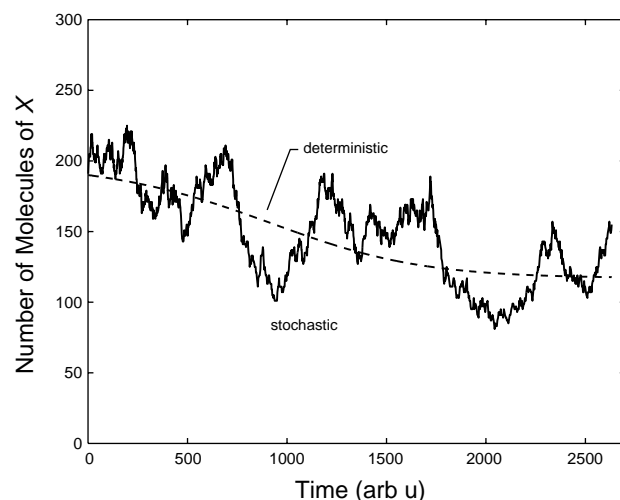

Figure 2. First simulation of the bistable process, eq 2: $N_X(0) = 190$, $N_A = 2 \times 10^5$, $N_B = 4 \times 10^5$, $k_1 = 7.72 \times 10^{-6}$, $k_2 = 6 \times 10^{-3}$, $k_3 = 2.66 \times 10^{-2}$, $k_4 = 167.5$.
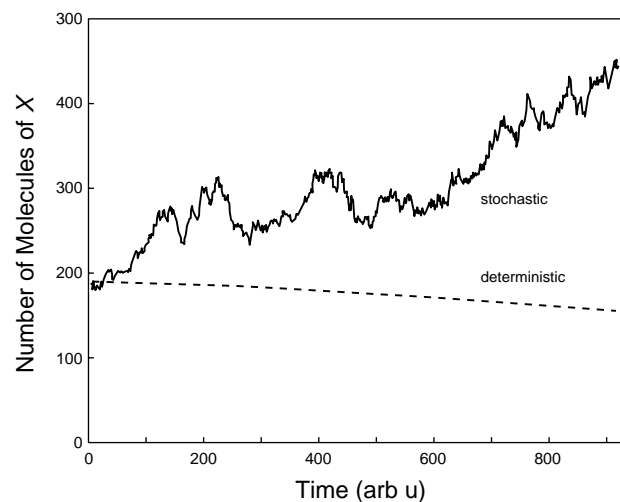

Figure 3. Second simulation of the bistable process, eq 2: parameters are the same as those shown in Figure 2.

also a random variable that can never be larger than 1 and it can only take the values -1, 0, and 1.

The reactions occur with a certain probability that depends on the reaction rate constants and on the number of molecules of each species at time t. Under this assumption, the probability, p, that a given molecule reacts in the interval $(t, t + dt)$ is $p = k_i dt$, where k_i is the reaction rate constant and may be interpreted as the probability that a reaction occurs in a very small time slice. In a system where n molecules can react in a given direction (n potential reactions), the probability that the reaction takes place in the interval $(t, t + dt)$ is:

$$p = nk_i dt \tag{4}$$

In our example, the number of potential reactions in $(t, t + dt)$ for the forward reaction is $N_X(t)$ and for the reverse reaction, N_B. Therefore the probabilities for the forward and reverse reactions in $(t, t + dt)$ are

$$p_1 = N_X(t)\,k_1 dt \tag{5}$$

and

$$p_2 = N_B k_2 dt \tag{6}$$

respectively. The conditional probability distribution of $dN_X(t)$ (conditional on the existence of $N_X(t)$ molecules in time t) is given in Table 1. $N_X(t)$ is, as in the deterministic case, the key variable when analyzing the evolution of the reaction through the stochastic approach.

In the general formulation (also valid for more complex systems) we define the two positive functions, $W_+[N_X(t)]$ and $W_-[N_X(t)]$, and the probabilities, $W_+[N_X(t)]dt$ and $W_-[N_X(t)]dt$, such that at time $(t + dt)$ the number of molecules $N_X(t + dt)$ is equal to $N_X(t) + 1$ and $N_X(t) - 1$, respectively. Therefore $W_+[N_X(t)]dt$ and $W_-[N_X(t)]dt$ are conditional probabilities (conditional on the value of $N_X(t)$). These functions are essential in the stochastic modeling and all the important results are derived from them. In our example, as can be seen in Table 1, these functions are:

$$W_+[N_X(t)] = k_2 N_B \tag{7}$$

$$W_-[N_X(t)] = k_1 N_X(t) \tag{8}$$

When formulating the stochastic approach for the time evolution of a chemical reaction, it is necessary to focus on the means (also called averages or expected values) of the two random variables $N_X(t)$ and $N_X(t + dt)$, symbolized by $\langle N_X(t)\rangle$ and $\langle N_X(t + dt)\rangle$, respectively. In probability theory the mean of a random variable is defined as the weighted sum of its values. It is shown in Appendix 1 of the Supplemental Material[w] that, for any reaction,

$$\frac{d\langle N_X(t)\rangle}{dt} = \langle W_+[N_X(t)]\rangle - \langle W_-[N_X(t)]\rangle \tag{9}$$

In some systems, such as the first example of this article, eq 9 is equivalent to the differential reaction rate equation of deterministic modeling. This occurs because $W_+[N_X(t)]$ and $W_-[N_X(t)]$ are linear functions of $N_X(t)$. In other systems, such as the second example of this article, the

Table 1. Conditional Probability Distribution of the Random Variable dN_X(t)

dN_X(t)	Probability
-1	$N_X(t)k_1 dt$
0	$1 - [N_X(t)k_1 dt + N_B k_2 dt]$
1	$N_B k_2 dt$

Schlögl reaction scheme, the coincidence is not total, but is reached after a series of approximations in which a large sample size is assumed. This is also intuitively reasonable in the sense that the deterministic behavior is equivalent to stochastic behavior with very large sample sizes *(8)*. The comparison of the deterministic and stochastic approaches for the Schlögl example is similar to that of the first example although mathematically more complex. More details are given in the Supplemental Material.[w]

In the stochastic approach, the probability distribution for $N_X(t)$, which gives for a given time point t the probability that $N_X(t)$ takes any of its possible values, is obtained through the so-called *master equation*. The master equation is a probabilistic computation of sources and wells for $N_X(t)$ that quantifies the time evolution of the system. In this article we do not include the development of the master equation, which can be seen in the excellent book by Gillespie *(10)*, but we do present an algorithm for the generation of trajectories of $N_X(t)$ (Appendix 2 in the Supplemental Material[w]). Through the generation of a large number of trajectories (also called sample paths) or time evolutions, one can estimate the marginal and joint distributions of $N_X(t)$: an approximation to the solution of the master equation. In this paper we just show one trajectory as an example. The problem would be completely solved if these distributions were known exactly. The final state is obtained from the condition

$$W_+[N_X(t)] = W_-[N_X(t)] \tag{10}$$

that is the result of equating the probabilities of moving upwards, increasing $N_X(t)$, and downwards, decreasing $N_X(t)$.

It turns out that the deterministic and stochastic conditions coincide, in such way that the set of possible final states is the same for both cases, even if sometimes an approximate alternative formula is used for the deterministic condition, which makes the results of both approaches slightly different (see Appendix 1 in the Supplemental Material[w]).

Obtaining the Time Evolution and Final State Values for the Two Examples

The calculation of the time evolution of the expected number of molecules (stochastic) or number of molecules (deterministic) and the calculation of the final state are two goals in both stochastic and deterministic modeling. Both goals for the two examples are discussed.

$X \rightleftharpoons B$ Process

In this example, taking into account eqs 5–6, we obtain,

$$\frac{d\langle N_X(t)\rangle}{dt} = k_2 N_B - k_1 \langle N_X(t)\rangle \tag{11}$$

which coincides exactly with the differential equation of the deterministic modeling for $N_X(t)$, eq 3. For the final state, the deterministic condition is,

$$dN_X(t)/dt = 0 \Rightarrow k_2 N_B = k_1 N_X(t)$$

which coincides with the stochastic condition:

$$W_+[N_X(t)] = W_-[N_X(t)] \Rightarrow k_2 N_B = k_1 N_X(t) \quad (12)$$

From these equations we can see that there is just one root, a unique value of $N_X(t)$ at the final state, N_S. The sign of the derivative $d[N_X(t)]/dt$ and the sign of the difference $W_+[N_X(t)] - W_-[N_X(t)]$ do not change, both are always positive or negative, depending on whether $N_X(0)$ is smaller than $k_2 N_B/k_1$ or larger than $k_2 N_B/k_1$. The final state value is then calculated for both the stochastic and deterministic approach as:

$$N_s = \frac{k_2 N_B}{k_1} \quad (13)$$

Schlögl Process

This is the example of a bistable process. By contrast with the previous example, the expressions for $d[N_X(t)]/dt$ and $d\langle N_X(t)\rangle/dt$ are not initially equivalent because $W_+[N_X(t)]$ and $W_-[N_X(t)]$ are not linear functions of $N_X(t)$. In fact, they are functions of $N_X^3(t)$ and $N_X^2(t)$, as is explained in Appendix 1 in the Supplemental Material.[w] To make both expressions equivalent, we have to make the approximations $\langle N_X^2(t)\rangle = \langle N_X(t)\rangle^2$ and $\langle N_X^3(t)\rangle = \langle N_X(t)\rangle^3$.

The final state is obtained for both approaches, using eq 14:

$$\frac{k_1 N_A N_X(t)[N_X(t) - 1]}{2!} + k_3 N_B$$
$$- \frac{k_2 N_X(t)[N_X(t) - 1][N_X(t) - 2]}{3!} \quad (14)$$
$$- k_4 N_X(t) = 0$$

though for the deterministic model an alternative approximate formula can be used, as shown in Appendix 1 in the Supplemental Material.[w] In this case eq 14 has three roots: two roots correspond to final states N_1 and N_3, and the other root to an unstable (also called barrier) state N_2, with $N_1 < N_2 < N_3$. The stochastic modeling predicts that $N_X(t)$ will evolve towards either of the two final states. Each possible evolution has a certain probability that depends on $N_X(0)$ and the reaction rate constants k_1–k_4. Given the initial values, two consecutive runs can evolve towards different final states. In the deterministic simulation, given the initial values, the system always follows the pathway that in the stochastic modeling has a probability larger than 0.5.

The lack of stability of the barrier state N_2 may be explained by considering that the stochastic evolution is guided by the conditional probability of moving upwards, $W_+[N_X(t)]$, or downwards, $W_-[N_X(t)]$. If $W_+[N_X(t)]$ is larger than $W_-[N_X(t)]$, $N_X(t)$ tends to increase and if the opposite is true, $N_X(t)$ tends to decrease. The relative probability of moving upwards,

$$\frac{W_+[N_X(t)]}{W_+[N_X(t)] + W_-[N_X(t)]} \quad (15)$$

as a function of the $N_X(t)$ value is shown in Figure 4. If we examine this probability in the neighborhood of the final state, $N_1 = 110$, we see that for values below 110 the relative probability is larger than 0.5, which means that if $N_X(t)$ deviates from 110 with smaller values, it will tend to rise. Similarly, for values larger than 110 the probability is lower than 0.5, thus if $N_X(t)$ deviates from 110 with larger values it will also tend to return. One could say that the state is a sort of magnet. The same occurs with the other final state $N_3 = 450$.

On the contrary, in the neighborhood of the unstable state, $N_2 = 215$, the behavior is the opposite. For values lower than 215 the relative probability is lower than 0.5, which means that if $N_X(t)$ deviates from 215 with lower values, it tends to deviate even further. For values higher than 215, the relative probability is higher than 0.5, thus, if $N_X(t)$ deviates from 215 with higher values, it also tends to deviate further.

Software Options

We have developed four MATLAB programs, *monostable.m, fmono.m, bistable.m,* and *fbistable.m,* that implement the deterministic and stochastic simulations for the first and second example, respectively. The output $N_X(t)$ is discrete (only integer values) for both approaches. The deterministic simulator solves, in each case, the differential reaction rate equation $dN_X(t)/dt = $ sources-wells, with the initial condition $N_X(t = 0) = N_X(0)$.

The stochastic simulator generates trajectories or sample paths, given the initial values, using the algorithm presented in Appendix 2 in the Supplemental Material.[w] The time between two consecutive changes in $N_X(t)$ is an exponential random variable. The run times are less than a minute for a few thousand consecutive reactions. The four MATLAB programs can be freely obtained at our Web site *(11)*.
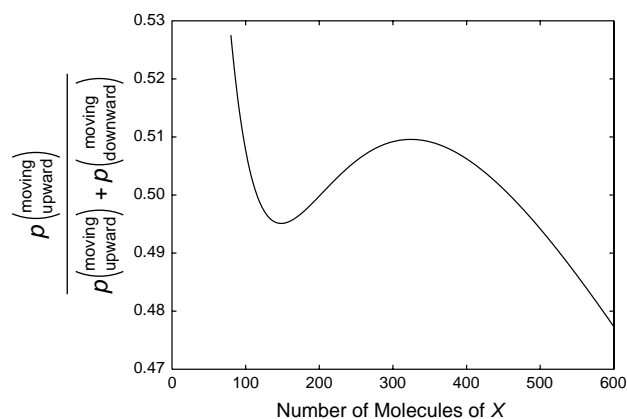

Figure 4. Relative probability of moving upwards.

$X \rightleftharpoons B$ Process: monostable.m *and* fmono.m

This process has four adjustable parameters, $N_X(0)$, N_B, k_1, and k_2, that must be provided by the user, as well as the number of reactions that will occur. The output is the graph of the time evolution of the number of molecules of X, $N_X(t)$ for both the deterministic and stochastic modeling.

Schlögl Process: bistable.m *and* fbistable.m

The input data are the values of the concentrations, $N_X(0)$, N_A, and N_B; the rate constants, k_1-k_4; and the number of reactions. The output is the time evolution of the number of molecules of X, $N_X(t)$, for both the deterministic and stochastic modeling. After repeating the simulation with different sets of values of the adjustable parameters, the students are able to discuss the characteristics of the deterministic or stochastic modeling of chemical reactions.

Results of the Simulations

Examples of the results obtained by students using the two simulation models are shown in Figures 1–3. These figures can be used to analyze the differences between both approaches and to relate the simulations with the corresponding real-life experiments.

The results obtained from the two simulations (deterministic and stochastic) of the $X \rightleftharpoons B$ process are illustrated in Figure 1. The input values were: $N_X(0) = 50$, $N_B = 5000$, $k_1 = 0.01$, and $k_2 = 1.6 \times 10^{-4}$. Both the deterministic and stochastic curves evolve towards the unique final state value $N_S = k_2 N_B / k_1 = 80$, as may be expected from the theoretical considerations described above. The only difference between the two curves is the fluctuations of the stochastic curve around the deterministic curve.

The students see that the deterministic evolution is unique, while the stochastic curve will change in each simulation. In fact, each result of the stochastic simulation is one of the many possible sample paths, all evolving towards the same final state in this example.

Simulations of the Schlögl process with the following input values, $N_X(0) = 190$, $N_A = 2 \times 10^5$, $N_B = 4 \times 10^5$, $k_1 = 7.72 \times 10^{-6}$, $k_2 = 6 \times 10^{-3}$, $k_3 = 2.66 \times 10^{-2}$, and $k_4 = 167.5$, are shown in Figures 2 and 3. There are two final states, $N_1 = 110$ and $N_3 = 450$, and one unstable state, $N_2 = 215$. In the stochastic modeling, the system can evolve towards either of the two final states, each evolution having a certain probability that is obtained from the $W_+[N_X(t)]$ and $W_-[N_X(t)]$ functions, as shown in Appendix 3 in the Supplemental Material.[W] With the initial value, $N_X(0) = 190$, the probabilities of evolving towards the two final states N_1 and N_3 are 0.596 and 0.404, respectively.

It is important to note that two stochastic simulations of the same problem, with the same initial values, can evolve towards different final states. This is the case represented in Figures 2 and 3: using the same input parameters and the same initial value $N_X(0) = 190$, there is evolution towards N_1 in Figure 2 and towards N_3 in Figure 3. In the deterministic simulation, $N_X(t)$ will always evolve towards the final state that in the stochastic modeling has a probability larger than 0.5. In this case it will evolve towards a value of 117, which is an approximation (see Appendix 1 in the Supplemental Material[W]) to the stochastic final state $N_1 = 110$.

Discussion

When the results shown in Figures 1–3 are analyzed in detail, a series of interesting questions arise:

- How important are the fluctuations of the stochastic curves?

- Is it possible that, under given input conditions, we have no clue about the final state value of our process?

- How are these results, obtained with reduced initial values of $N_X(0)$ (values like 190), related to real-life experiments where, in most cases, the number of molecules we are dealing with is enormous (for instance 10^{20})?

Students can easily obtain information about the importance of the fluctuations by simply repeating the simulation with different initial values of N_X. They will observe that the fluctuations are only important when $N_X(0)$ is small; however, as $N_X(0)$ increases, both curves (stochastic and deterministic) tend to be the same. A similar result may be seen in the book by Steinfeld, Francisco, and Hase *(8)*. This result is explained by Gillespie *(10)* showing that the fluctuations in $N_X(t)$ around $\langle N_X(t) \rangle$ can be calculated as,

$$\approx \frac{\langle N_X(t) \rangle^{1/2}}{\langle N_X(t) \rangle} = \frac{1}{\langle N_X(t) \rangle^{1/2}}$$

which tends to zero as $N_X(t)$ increases *(10)*.

Concerning the uncertainty on the final state that will be achieved in a bistable process, students should know that processes actually exist in which it is impossible to predict the final state with certainty. This behavior can be seen in some in vivo biochemical processes, as has been pointed out by several authors *(7, 8)*.

However, is this a frequent behavior in nature? It can be shown that in a bistable process the uncertainty on the final state depends on the number of reacting molecules. The uncertainty associated with evolving towards one or the other of the two possible final states can be measured through the amplitude of the fluctuations around the barrier or unstable state. The larger the fluctuations are, the greater the uncertainty *(10)*.

We have seen that the relative fluctuations around a $N_X(t)$ value are of the order of $\langle N_X(t) \rangle^{-1/2}$; that is, the uncertainty on the final state decreases as the number of reacting molecules increases. When the number of molecules of the system is very large, which is the most frequent situation in practice, the stochastic modeling indicates that the probability of reaching each one of the final states will be practically one or practically zero. In other words, only one final state is possible in these cases. This is also the final state that will be predicted by the deterministic models.

Both the stochastic and the deterministic simulation give the same predictions when the initial number of reacting molecules is large. The stochastic effects are relevant only when the initial number of reacting molecules is very small. However, students should bear in mind that there exist processes in which the stochastic effects are relevant. In these cases the time evolution of the system depends on the behavior of a very small number of molecules *(7, 8)*. The be-

havior of such systems can not be accurately predicted by the deterministic models.

Does this mean that we should ignore deterministic modeling in the future? The answer that results from the previous discussion is that the deterministic modeling describes the average behavior of the system, and this average behavior is in most cases a suitable representation of chemical processes. Another advantage of deterministic modeling is its relative mathematical simplicity. The stochastic modeling describes accurately a wider range of chemical processes. Both approaches are interesting and complementary from the educational point of view.

Conclusion

The two approaches (deterministic and stochastic) used in modeling chemical reactions have a different starting point. The deterministic approach does not take into account the stochastic nature of chemical reactions—that each individual reaction is an event that takes place with a certain probability. Thus, deterministic models give only the average behavior of the system and can not predict the stochastic effects that appear in real life in some chemical and biological processes. This does not mean that we must forget the deterministic models because they give inaccurate predictions. The average behavior is a suitable representation of the system evolution in most cases, especially when the number of molecules involved is large. In contrast, only the stochastic models can predict stochastic effects and give a more accurate representation of the system evolution when this evolution depends on the behavior of a small number of molecules.

From an educational point of view, each simulation approach has its advantages and disadvantages. The determin-

istic approach is more widely used in the teaching of chemical kinetics, probably as a result of its greater mathematical simplicity and its closer relation with the classical (nonnumerical) approach to the modeling of chemical reactions. However, the above discussion indicates that the inclusion of stochastic modeling in the teaching of chemical kinetics can be advantageous and that the simultaneous use of stochastic and deterministic models in the simulation of chemical reactions will allow the students to achieve a better understanding of chemical dynamics.

^WSupplemental Material

Appendices 1–3 are available in this issue of *JCE Online*.

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