MATCH
Communications in Mathematical and in Computer Chemistry

MATCH Commun. Math. Comput. Chem. **71** (2014) 265-277

ISSN 0340 - 6253

Application of Stochastic Differential System in Chemical Reactions via Simulation

B. Kafash[1], R. Lalehzari[1], A. Delavarkhalafi[2], E. Mahmoudi[2]

[1,2] *Faculty of Mathematics, Yazd University, Yazd, P.O. Box 89197/741, Iran.*
[1] *Emam Javad Higher Education Institute, Yazd, Iran.*

(Received June 25, 2012)

Abstract

Stochastic process models play a prominent role in a range of application areas, including biology, chemistry, epidemiology, mechanics, microelectronics, economics, and finance. In mathematical modeling, if we use stochastic systems then we will assume that the system follows a probabilistic rule and the future behavior of the system will not be known for sure. Idea of modeling chemical reactions in terms of ordinary and stochastic differential equations can be exposed to a range of modern ideas in applied and computational mathematics. In this paper, we will introduce some fundamental concepts of stochastic processes and simulate them with R saftware. Also, we peresent a numerical solution of chemical Langevin equation as a stochastic differential system with applications in Chemistry and Physics.

1 Introduction

Stochastic process models play a prominent role in a range of application areas, including biology, chemistry, epidemiology, mechanics, microelectronics, economics, and finance. In mathematical modeling, if we use stochastic systems then we will assume that the system follows a probabilistic rule and the future behavior of the system will not be known for sure.

First, we will introduce some fundamental concepts of stochastic processes such as Brownian Motion, Ornstein-Uhlenbeck (OU) process. Then we study Stochastic differential equations (SDEs) and Euler-Maruyama method as a numerical solution of the SDE and Langevin equation as an example of an Ornstein-Uhlenbeck process. This is a stochastic differential equation with application in Chemistry.

Then we are concerned with a process that involves N different types of molecules, or chemical species. These molecules may take part in one or more of M types of chemical reactions; for

example, we may know that “a molecule of species A and a molecule of species B can combine to create a molecule of species C.” In principle, we could start with a position and a velocity for each molecule and let the system evolve under appropriate laws of physics, keeping track of collisions between molecules and the resulting interactions. However, this molecular dynamics approach is typically too expensive, computationally, when the overall number of molecules is large or the dynamics over a long time interval are of interest [8, 10].

2 Preliminaries

In this section, some basic concepts of stochastic processes which are used in the next sections are reviewed briefly [5, 10]

- Probability Space $(\Omega, \mathcal{A}, \mathbb{p})$: A probability space or a probability triple is a mathematical construct that models a real-world process (or "experiment") consisting of states that occur randomly.
  1. Ω (Sample Space): Sample space is the set of all possible outcomes.
  2. $\mathcal{A}$ ($\sigma-$ algebra): A sigma-algebra is a collection of all and only events (not necessarily elementary) we would like to consider.
  3. $\mathbb{p}$ (Probability Measure): Is a function returning an event's probability.
- With Probability 1: Also known as almost surely. The probability of an event occuring tends to 1 given some limit. Note that this differs from surely in that surely indicates that no other event is possible, while almost surely indicates that other events become less and less likely.
- Random Variables: A random variable X with values in the set E is a function which assigns a value $X(\omega)$ in E to each outcome ω in Ω.
- Stochastic Process: A real valued stochastic process $X(t,\omega), t \geq 0, \omega \in \Omega$ is just a sequence of real valued functions (random variables), $X_t, t \geq 0$ $\{X_t, t \geq 0\}$ on Ω.

Essentially, the definition says that the outcomes of the experiment are all functions of time. Just as a random variable assigns a number to each outcome s in a sample space Ω, a stochastic process assigns a sample function to each outcome s.

Brief Introduction into Using R

R is an integrated suite of software facilities for data manipulation, simulation, calculation and graphical display. It handles and analyzes data very effectively and it contains a suite of operators for calculations on arrays and matrices. In addition, it has the graphical capabilities

for very sophisticated graphs and data displays. Finally, it is an elegant, object-oriented programming language.

R is an independent, open-source, and free implementation of the S programming language. Today, the commercial product is called S-PLUS and it is distributed by the Insightful Corporation. The S language, which was written in the mid-1970s, was a product of Bell Labs and was originally a program for the Unix operating system. R is available in Windows and Macintosh versions, as well as in various flavors of Unix and Linux. Although there are some minor differences between R and S-PLUS (mostly in the graphical user interface), they are essentially identical.

The R project was started by Robert Gentleman and Ross Ihaka (that's where the name "R" is derived) from the Statistics Department in the University of Auckland in 1995. The R project web page is http://www.r-project.org The current version of R is 2.12.2. New versions are released periodically. There are a number of packages supplied with R (called "standard" packages) and many more are available through the CRAN family of Internet sites http://cran.um.ac.ir.

3 Brownian Motion and Its Simulation

The long studied model known as Brownian motion, also known as a Wiener process, is named after the English botanist Robert Brown. In 1827, Brown described the unusual motion exhibited by a small particle totally immersed in a liquid or a gas. In 1900, the French mathemetician Bachelier independently introduced Brownian motion to model the price movements of stocks and commodities. In 1905, Albert Einstein was able to explain this motion mathematically. He assumed that the immersed particle was continuously bombarded by molecules of the surrounding medium. In a series of papers originating in 1918, Norbert Wiener provided a mathematically concise definition and other mathematical properties of Brownian Motion.

Definition 1 *A stochastic process* $W(t)$ *is said to follow a standard Brownian motion on* $[0,T]$ *if it satisfies the following:*

I. $W(0)=0$ *(with probability 1).*

II. *For* $0 \le s < t \le T$ *the random variable given by the increment* $W(t)-W(s)$ *is normally distributed with mean zero and variance* $t-s$ *; equivalently,*

$W(t)-W(s) : \sqrt{t-s}\, N(0,1)$, *where* $N(0,1)$ *denotes a normally distributed random variable with zero mean and unit variance.*

III. *For* $0 \le s < t < u < v \le T$ *the increments* $W(t)-W(s)$ *and* $W(v)-W(u)$ *are independent.*

IV. $W(t)$ *is almost surely continuous.*

For computational purposes it is useful to consider discretized Brownian motion, where $W(t)$ is specified at discrete t values. We thus set $\delta t = T/N$ for some positive integer N and let W_j denote $W(t_j)$ with $t_j = j\delta t$. Condition 1 says $W(0) = 0$ with probability 1, and conditions 2 and 3 tell us that

$$W_{j+1} = W_j + dW_{j+1}, \quad j = 0,1,2,\cdots,N, \tag{1}$$

where each dW_j is an independent random variable of the form $\sqrt{\delta t}\, N(0,1)$.

In program 1, we use R software to simulate discretized Brownian motion over $[0,1]$ with $N = 500$. Here, the random number generator rnorm is used, in fact, rnorm produces an independent "pseudorandom" number from the $N(0,1)$ distribution.

Program 1.

```
#     Brownian path simulation
T = 1                    #   T is the maturity ( time belongs to [0,T])
N = 500                  #   N is the length of the sample path for Brownian Motion
delta = T/N              #   delta is the increment of time period
W = rep(0,times=N)   #   preallocate arrays for efficiency
W[1]=0                   #   first approximation outside the loop since W(0)=0 is not allowed
t=rep(0,times=N)
t[1]=0
for (j in 1:N)
        {
        W[j+1]=W[j]+sqrt(delta)*rnorm(1)      #   general increment
        t[j+1]=t[j]+delta
        }
plot(t,W,type="l")                    #   plot W against t
```

Finally, the diffusion sample path can be plotted and results for four sample paths are displayed in Figure 1(a) using $N = 500$ and $T = 1.0$. In Figure 1(b), the variation of the fine

structure of the sample path is displayed, with time step size using subsets of the same random sample state. The sample paths in this case differ markedly since the sample subsets are quite different in quantity, being $N = 1000,100$ and 10 random sample points for $\delta t = 10^{-3}, 10^{-2}$ and 10^{-1}, respectively. note that for the purpose of visualization, the discrete data has been joined by straight lines.

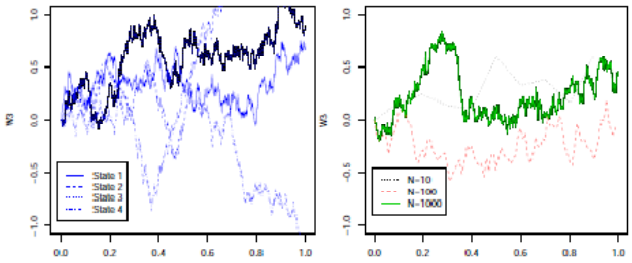

Figure 1. (a) Diffusion sample paths using four random states. (b) Diffusion sample paths using three different time steps.

4 Stochastic Differential Equations

In recent years, the application of SDEs in different sciences has increased rapidly. Often the analytic solution of these differential equations is not available. The important difference between SDE and ordinary differential equation(ODE) is the existence of Wiener Process.

Here we introduce a type of stochastic differential equations driven by Brownian motion. The general form of SDE is:

$$dX(t) = b(t, X(t))dt + \sigma(t, X(t))dW(t), \quad X(0) = X_0, \tag{2}$$

which looks almost like an ODE. However, as usual, the "Itˆo differentials" are not sensible mathematical objects in themselves; rather, we should see this expression as suggestive notation for the Itˆo process

$$X(t) = X_0 + \int_0^t b(s, X(s))ds + \int_0^t \sigma(s, X(s))dW(s). \tag{3}$$

If there exists a stochastic process $X(t)$ that satisfies this equation, we say that it solves the stochastic differential equation.

Definition 2 *In a stochastic differential equation, $b(t, X(t))$ is drift coefficient and $\sigma(t, X(t))$ is diffusion coefficient. In additive noise stochastic differential equation, σ is only depended on t and in multiplicative noise stochastic differential equation, σ is depended on t and $X(t)$.*

Example 1.

Consider the stochastic differential equation

$$dX(t) = X(t)dW(t), \quad X(0) = 1, \tag{4}$$

where $W(t)$ is a scalar Wiener process. According to Ito's formula, the solution of the stochastic differential equation is

$$X(t) = e^{W(t)-\frac{1}{2}} \tag{5}$$

and not what might seem the obvious guess, namely $\hat{X}(t) = e^{W(t)}$.

Example 2.

(scalar linear equation) *Consider the scalar linear stochastic differential equation*

$$dX(t) = aX(t)dt + bX(t)dW(t), \quad X(0) = X_0 \tag{6}$$

driven by a scalar Wiener process $W(t)$, with a and b constants. This stochastic differential equation is said to have multiplicative noise. We can in fact analytically solve this equation, the solution is

$$X(t) = X_0 \exp((a - \frac{1}{2}b^2)t + bW(t)). \tag{7}$$

Definition 3. *Let $X(t)$ be a solution to Equation (6), is called a geometric Brownian motion.*

Example 3.

(Stock prices) *Let $X(t)$ denote the (random) price of a stock at time $t \geq 0$. A standard model assumes that $\frac{dX(t)}{X(t)}$, the relative change of price, evolves according to the SDE*

$$\frac{dX(t)}{X(t)} = \lambda dt + \mu dW(t), \tag{8}$$

for certain constants $\lambda > 0$ and μ, called respectively the drift and the volatility of the stock. In other words,

$$dX(t) = \lambda X(t)dt + \mu X(t)dW(t), \quad X(0) = X_0, \tag{9}$$

where X_0 is the starting price. Using once again Ito's formula we can check that the solution is

$$X(t) = X_0 \exp((\lambda - 0.5\mu^2)t + \mu W(t)). \tag{10}$$

5 Examples and Simulations

This section presents two famous examples of diffusions: Geometric Brownian motion and the Ornstein-Uhlenbeck process. The SDE is solved analytically, and numerical approximations are used to simulate and plot sample paths of the solution.

5.1 Geometric Brownian Motion

Definition 4 *Let* $W(t)$ *be a standard Brownian motion. Then* $\lambda t + \mu W(t)$ *is a Brownian motion, and the stochastic process*

$$G(t) = \exp(\lambda t + \mu W(t)), \tag{11}$$

is called a geometric Brownian motion.

Geometric Brownian motion $G(t)$ is an important model for stock prices. For each $t > 0$, the G_t has a lognormal distribution whose probability density function is

$$\phi(z) = \frac{1}{\mu z\sqrt{2\pi t}} \exp(-\frac{(\ln z - \lambda t)^2}{2\mu^2 t}),\ z \geq 0 \tag{12}$$

and has expected value and variance as follows:

$$E[G(t)] = \exp(\lambda t + \mu^2 t/2),$$

$$V[G(t)] = \exp(2\lambda t + 2?\mu^2 t) - \exp(2\lambda t + \mu^2 t).$$

In addition, the first passage time that a geometric Brownian motion $G(t)$ reaches the barrier $x > 1$ is just the time that the Brownian motion with drift λ and diffusion μ reaches lnx.

In Program 2 we evaluate the stock model function $u(W(t))$, Equation (10) in Example 3, along $M = 1000$ discretized Brownian paths with $\lambda = \frac{9}{8}$ and $\mu = \frac{1}{2}$.

Program 2.

```
#     Function along a Brownian path
T = 1; N = 500; dt = T/N; t = seq(dt,1,dt)
M = 1000; mu=0.5; lambda=9/8; X0=1
dW=sqrt(dt)*matrix(rnorm(M*N),nrow=M)
S=rep(0,N)
y=matrix(rep(0,6*(N+1)),nrow=6)
for (j in 1:6)
y[j,]=rep(0,N+1)
k=ceiling(runif(5, min=0, max=1000))
for (j in 1:M)
S=S+X0*exp((lambda-0.5*mu 2)*t+mu*cumsum(dW[j,]))
```

```
time=c(0,t)
U=c(1,S/M)
plot(time,U,type="s",col=1)
y[1,]<-U
for (i in 2:6)
    {
     y[i,]<-(c(1,X0*exp((lambda-0.5*mu 2)*t+mu*cumsum(dW[k[i],]))))
     lines(time,yy[i,], type="l",lty=1,col=2)
    }
leg.names<-c("mean of 1000 paths","5 individual paths")
legend(locator(1),leg.names)
```

Since answer of the stochastic differential equation is a stochastic process we solve it with 1000 different Wiener processes and use $W(t)=\frac{1}{M}\sum_{i=1}^{M}W_i(t)$ to find the numerical solution of SDE.

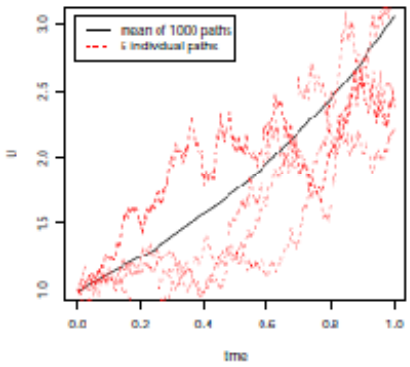

Figure 2. The function $u(W(t))$ averaged over 1000 discretized Brownian paths and along 5 individual paths.

The expected value of this solution can be seen as the center line with a smooth appearence (see Figure 2). Notice that although $u(W(t))$ is nonsmooth along the individual paths, the expected value of the solution appears to be smooth. This can be established by noting that the properties of the Brownian motion require the expected value of $W(t)$ to be zero. Therefore, the expected value of $u(W(t))$ is solely dependent on the drift and not the volatility. In this example, the expected value turns out to be $e^{9t/8}$. The average of $u(W(t))$ over these paths is plotted with a solid black line. Five individual paths are also plotted using a dashed red line.

5.2 Ornstein-Uhlenbeck Process

The Ornstein-Uhlenbeck process was proposed by Leonard Ornstein and George Eugene Uhlenbeck (1930) in a physical modelling context, as an alternative to Brownian Motion, where some kind of mean reverting tendency is called for in order to adequately describe the situation being modelled. Since the original paper appeared, the model has been used in a wide variety of applications areas. In Finance, it is best known in connection with the Vasicek (1977) interest rate model. However, to set the scene we will briefly discuss the standard (Gaussian) OU process, driven by Brownian Motion, and concentrate thereafter on some extensions that have recently attracted attention, especially in the financial modelling literature. In mathematics, the Ornstein-Uhlenbeck process, also known as the mean-reverting process, is a stochastic process $X(t)$ given by the following stochastic differential equation:

$$dX(t) = -cX(t)dt + \sigma dW(t), \qquad X(0) = X_0, \tag{13}$$

where $c > 0$ and $\sigma > 0$ are parameters and $W(t)$ denotes the Brownian motion.

The Ornstein-Uhlenbeck process is one of several approaches used to model (with modifications) interest rates, currency exchange rates, and commodity prices stochastically. Here are some examples of OU process with different choices of σ, $c = 0.1$ and $X(0) = 2$. Langevin equation is also an example of an Ornstein-Uhlenbeck process. This is a stochastic differential equation with application in Chemistry and Physics.

Example 4 ***(Langevin equation)*** *As we have seen, the Brownian motion of a pollen particle suspended in a fluid flow obeys the following equation of motion for its velocity* $X(t)$*:*

$$dX(t) = -aX(t)dt + \sqrt{b}dW(t), \tag{14}$$

where a *and* b *are constants, and* $W(t)$ *is a scalar Wiener process. This type of stochastic differential equation is said to have additive noise.*

Program 3

```
#     Ornstein-Uhlenbeck path simulation
T = 1                    #    T is the maturity ( time belongs to [0,T])
N = 500                  #    N is the length of the sample path for Ornstein-Uhlenbeck Process
c=0.1
sigma=0.5
X = rep(0,N)
X[1]=2
    for (j in 1:N)
    {
     X[j+1]=X[j]-c*X[j]+sigma*rnorm(1)        #     general increment
    }
plot(X,type="l")
```

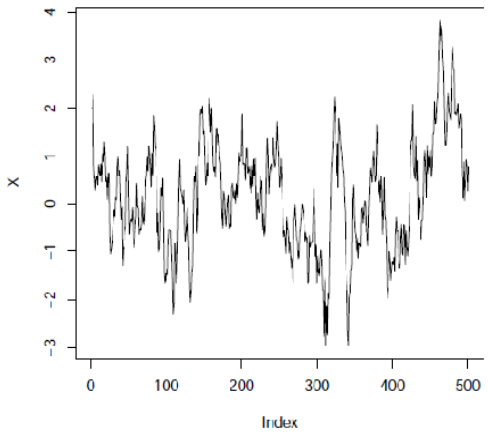

Figure 3. Sample path of OU process for $c = 0.1,\ \sigma = 0.5$

6 Chemical Reactions

In this section, chemical reactions between molecules are modeled in a stochastic manner. It is shown how an SDE model can be developed using the two modeling procedures. It is assumed that a fixed volume contains a uniform mixture of d different chemical species that interact through m different chemical reactions. The reaction rates are either proportional to the rates that the molecules collide or, if the reaction is spontaneous, the reaction rate is just proportional to the number of molecules of the particular chemical species. Given the initial numbers of molecules of the d different chemical species, the objective is to find the molecular population levels at a later time. To illustrate the modeling procedure for chemical reactions, it is useful to consider a specific problem. Therefore, suppose that there are three chemical species S_1, S_2 and S_3 interacting through molecular collisions or spontaneously in the four ways described in Table 1 [13]. In Table 1 μ_1, μ_2, μ_3 and μ_4 are reaction rate constants and X_1, X_2 and X_3 are the number of molecules of species S_1, S_2 and S_3, respectively. Using the second modeling procedure gives the chemical Langevin systems [14].

Table 2: Probabilities for reactions among three chemical species [13].

Reaction	Probability
$S_1 + S_2 \to S_3$	$p_1 = \mu_1 X_1 X_2 \Delta t$
$S_3 + S_2 \to S_1$	$p_2 = \mu_2 X_3 \Delta t$
$2S_2 + S_3 \to 2S_1$	$p_3 = \mu_3 X_2^2 X_3 \Delta t/2$
$2S_1 + 2S_2 \to S_3$	$p_4 = \mu_4 X_1^2 \Delta t/2$

6.1 A K^+ channel

Transformations of human ether a-go-go related gene (HERG) encoded K^+ channels between three closed states $(C_1;C_2;C_3)$, one open state (O) and one inactivation state (I) [15]. It models as $n=5$ chemical species $(C1;C2;C3;O;I)$ reacting through $m=10$ reaction channels (See Fig. 4)

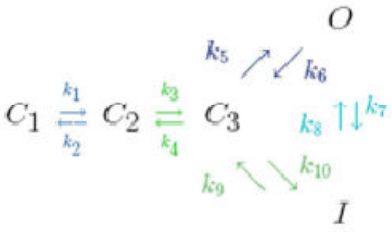

Figure 4: A K^+ channel

The chemical Langevin equation:

$$d\begin{pmatrix} X_1 \\ X_2 \\ X_3 \\ X_4 \\ X_5 \end{pmatrix} = \begin{bmatrix} -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & -1 & 1 & 0 & 0 & 1 & -1 \\ 0 & 0 & 0 & 0 & 1 & -1 & -1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & -1 & 1 \end{bmatrix} \begin{pmatrix} k_1 X_1 \\ k_2 X_2 \\ k_3 X_2 \\ k_4 X_3 \\ k_5 X_3 \\ k_6 X_4 \\ k_7 X_4 \\ k_8 X_5 \\ k_9 X_5 \\ k_{10} X_3 \end{pmatrix} dt + g(X) dW(t).$$

Which

$$g(X)dW(t)=\begin{bmatrix} -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & -1 & 1 & 0 & 0 & 1 & -1 \\ 0 & 0 & 0 & 0 & 1 & -1 & -1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & -1 & 1 \end{bmatrix}$$

$$\begin{bmatrix} \sqrt{k_1 X_1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \sqrt{k_1 X_1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \sqrt{k_3 X_2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \sqrt{k_4 X_3} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \sqrt{k_5 X_3} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \sqrt{k_6 X_4} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \sqrt{k_7 X_4} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sqrt{k_8 X_5} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sqrt{k_9 X_5} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sqrt{k_{10} X_3} \end{bmatrix} \begin{pmatrix} dW_1(t) \\ dW_2(t) \\ dW_3(t) \\ dW_4(t) \\ dW_5(t) \\ dW_6(t) \\ dW_7(t) \\ dW_8(t) \\ dW_9(t) \\ dW_{10}(t) \end{pmatrix}$$

For the purpose of illustration, the following parameters have been chosen:

Rate constants: $k_1 = \cdots k_{10} = 0.1$,

Initial state: $(100; 50; 100; 50; 100)$

Time horizon: $[0; 5]$, *step size*: 0.005.

We simulate this example in R with the Euler Maruyama method. Numerical solution in final time is obtained as follow:

$$X(5) = (12.95, 24.12, 105.85, 20.01, 68.72, 61.30)$$

7 Conclusion

This article is designed to give readers a brief and practical introduction to the concept "Stochastic Processes" with a minimum of technical detail, also the usages of stochastic process discussed. Brownian motion, geometric Brownian motion, stochastic differential equations, stochastic integration, Ornstein-Uhlenbeck process and SDE were explained simply, also by using R, simulated them. Finally, we have stated numerical results of chemical Langevin equation that don't have any exact solution.

References

[1] D. J. Higham, An algorithmic introduction to numerical simulation of stochastic differential equations, *SIAM Rev.* **43** (2001) 525–546.

[2] W. J. Owen, *The R Guide*, 2007, http://cran.r-project.org/doc/contrib/Owen-TheRGuide.pdf.

[3] W. P. Krijnen, *Applied Statistics for Bioinformatics using R*, 2009, http://cran.r-project.org/doc/contrib/Krijnen-IntroBioInfStatistics.pdf

[4] H. Quené, Statistics with R and S-plus, *Third Workshop on Experimental Methods in Language Acquisition Research (EMLAR)*, 2006, http://cran.r-project.org/doc/contrib/Quene.pdf

[5] B. Oksendal, *Stochastic Differential Equations*, Springer–Verlag, Berlin, 2003.

[6] P. E. Kloeden, E. Platen, *Numerical Solution of Stochastic Differential Equations*, Springer–Verlag, Berlin, 1992.

[7] L. E. Evans., *An Introduction to Stochastic Differential Equations*, http://math.berkeley.edu/evans/

[8] F. B. Hanson, *Applied Stochastic Processes and Control for Jump–Diffusions: Modeling, Analysis and Computation*, Univ. Illinois, Chicago, 2007.

[9] P. E. Protter, *Stochastic Integration and Differential Equations*, Springer, Berlin, 2004.

[10] S. M. Ross, *Stochastic Processes*, Wiley, New York, 1983.

[11] B. Kafash, A. Delavarkhalafi, E. Mahmoudi, R. Lalehzari, *Stochastic Processes in Different Sciences: Application and Simulation*, Proceeding of the 8th Seminar on Probability and Stochastic Processes, Univ. Guilan, Rasht, 2011, pp. 211–218.

[12] B. Kafash, R. Lalehzari, *Simulate Stochastic Processes with R and Their Applications in Science and Engineering*, The 8th Iranian International Workshop on Applied Stochastic Processes, Shiraz Univ., Shiraz, 2011.

[13] E. Allen, *Modeling with Itô Stochastic Differential Equations*, Springer, Berlin, 2007.

[14] D. T. Gillespie, Approximate accelerated stochastic simulation of chemically reacting systems, *J. Chem. Phys.* **115** (2001) 1716–1733.

[15] T. Brennan, M. Fink, B. Rodriguez, Multiscale modelling of drug–induced effects on cardiac electrophysiological activity, *Eur. J. Pharm. Sci.* **36** (2009) 62–77.