J. Appl. Math. & Informatics Vol. **31**(2013), No. 3 - 4, pp. 457 - 467
Website: http://www.kcam.biz

STOCHASTIC DIFFERENTIAL EQUATION MODELS FOR EXTRACELLULAR SIGNAL-REGULATED KINASE PATHWAYS

S.M. CHOO* AND Y.H. KIM†

Abstract. There exist many deterministic models for signaling pathways in systems biology. However the models do not consider the stochastic properties of the pathways, which means the models fit well with experimental data in certain situations but poorly in others. Incorporating stochasticity into deterministic models is one way to handle this problem. In this paper the way is used to produce stochastic models based on the deterministic differential equations for the published extracellular signal-regulated kinase (ERK) pathway. We consider strong convergence and stability of the numerical approximations for the stochastic models.

AMS Mathematics Subject Classification : 34A34, 34A99, 39A50, 92B05.
Key words and phrases : Deterministic models, stochastic differential equations. numerical solutions, boundedness, convergence, stability.

1. Introduction

Signal transduction through the Ras-Raf-MEK-ERK pathway (or ERK pathway for short) is essential for many cellular processes, including growth, cell-cycle progression, differentiation, and apoptosis. In order to elucidate the hidden dynamics of these feedback mechanisms and to identify the functional role of RKIP, an experimentally validated deterministic model for ERK pathway is provided in [4]. The results obtained from the equations are fitted with some experimental data; however, the system of ordinary differential equations(ODEs) do not reflect stochastic nature of the ERK pathway. Thus the deterministic model may be modified into a more realistic model including stochastic properties.

For incorporating stochasticity into the deterministic model, Itô stochastic differential equations(SDEs) are introduced based on the ODEs; some of the

Received January 9, 2013. Revised March 7, 2013. Accepted March 8, 2013. *Corresponding author. †The present research has been conducted by the Research Grant of Kwangwoon University in 2013.

parameters in the ODEs are replaced by those having stochasticity and the concentrations are modified to the corresponding random variables.

For the completeness of this paper, the ODEs for the ERK pathway is given by

$$\frac{d[RasGTP]}{dt} = \frac{K_{cat_1} u(t) \left(\overline{Ras} - [RasGTP]\right)}{\left(K_{mk_1} + \overline{Ras} - [RasGTP]\right)\left(1 + \left(\frac{[ERK]}{K_{i\_erk}}\right)^{3.2}\right)} - \frac{V_{\max_1}[RasGTP]}{K_{mp_1} + [RasGTP]}$$

$$\frac{d[Raf]}{dt} = \frac{K_{cat_2}\left(\overline{Raf} - [Raf]\right)[RasGTP]}{K_{mk_2} + \overline{Raf} - [Raf]} - \frac{V_{\max_2}[Raf]}{K_{mp_2} + [Raf]}$$

$$\frac{d[MEK]}{dt} = \frac{K_{cat_3}\left(\overline{MEK} - [MEK]\right)[Raf]}{K_{mk_3}\left(1 + \left(\frac{\left(\overline{RKIP} - [RKIP]\right)}{K_{i\_rkip}}\right)^{2.3}\right) + \overline{MEK} - [MEK]} - \frac{V_{\max_3}[MEK]}{K_{mp_3} + [MEK]}$$

$$\frac{d[ERK]}{dt} = \frac{K_{cat_4}\left(\overline{ERK} - [ERK]\right)[MEK]}{K_{mk_4} + \overline{ERK} - [ERK]} - \frac{V_{\max_4}[ERK]}{K_{mp_4} + [ERK]}$$

$$\frac{d[RKIP]}{dt} = \frac{K_{cat_5}\left(\overline{RKIP} - [RKIP]\right)[ERK]}{K_{mk_5} + \overline{RKIP} - [RKIP]} - \frac{V_{\max_5}[RKIP]}{K_{mp_5} + [RKIP]}, \qquad (1)$$

where $[RasGTP], [Raf], [MEK]$ and $[ERK]$ denote the concentrations of the activated proteins Ras, Raf, MEK and ERK, respectively. $[RKIP]$ denotes the concentrations of the phosphorylated RKIP. The upper bar of each protein kinase (e.g., $\overline{ERK}$) means the total amount of the protein which is assumed constant. $u(t)$ denotes the activating stimulation. The other details of the ODEs can be found in [4].

The stochastic model is constructed by incorporating stochasticity to the deterministic model (1). To our knowledge, there are no approaches to incorporate stochasticity into the ERK pathway model. In this paper, the SDEs and its numerical scheme are given in Section 2 as well as definitions necessary for numerical analysis. In the last two sections, error estimates and numerical stability are obtained.

2. Notations and Definitions

Incorporate stochasticity into some of the parameters for modifying the ODEs (1), denoted by $\frac{dX(t)}{dt} = a(X(t))$, into the Itô SDEs of the form

$$dX(t) = a\left(X(t)\right)dt + \sum_{j=1}^{m} b_j\left(X(t)\right)dW_j(t)\ ,\ 0 \le t \le T \qquad (2)$$

where $W_j(t)$ are independent and real valued standard Wiener processes and $a, b_j : R^5 \to R^5$. Stochastic processes $X(t)$ with values in R^5 are $\mathcal{F}_t$-measurable and $\mathcal{F}_t$ denotes the increasing family of σ-algebras(the augmented filtration) generated by the random variables $W_j(s), 0 \leq s \leq t$. If we denote $a = (a_1, \cdots, a_5)$, $a_i(X(t)) = K_{cat_i} a_{i1}(X(t)) - V_{max_i} a_{i2}(X(t))$ in the ODEs (1) and change V_{max_i} $(1 \leq i \leq 5)$ to $V_{max_i} + \xi_1$ with the white noise processes ξ_1 for obtaining (2), respectively, then $m = 1$ and $b_1(X(t)) = (a_{11}(X(t)), \cdots, a_{51}(X(t)))$ in (2).

$E(X) = (E(X_1), \cdots, E(X_5))$ is the expectation of $X = (X_1, \cdots, X_5)$. Let $\| \ \|$ and $\langle , \rangle$ denote the Euclidean norm and inner product in R^5. For simplicity, $E \|X\|^2$ is used to mean $E\left(\|X\|^2\right)$.

The equation (2) constructed from the ODEs (1) has a unique, mean square bounded strong solution $X(t)$, which is a function of the initial value $X(0)$ and the values $W_j(s)(1 \leq j \leq m, 0 \leq s \leq t)$ (See [2] for the definition of strong solution and the existence and uniqueness).

To find time discrete approximations corresponding to the equation (2) the time interval $[0, T]$ is uniformly divided into $t_0 = 0 < t_1 < \cdots < t_N = T$ with the time-step size $\Delta = \frac{T}{N}$ for a natural number N.
Consider the one-step numerical scheme for the SDEs (2)

$$Y_{n+1} = Y_n + a\left(Y_n\right)\Delta + \sum_{j=1}^{m} b_j\left(Y_n\right)\Delta W_j\left(t_n\right), \tag{3}$$

where $Y_0 = X(0)$ and Y_{n+1} is the numerical approximation of $X(t_{n+1})$ at time $t_{n+1} = (n+1)\Delta$ and $\Delta W_j(t_n) = W_j(t_{n+1}) - W_j(t_n)$, $n = 0, 1, \cdots, N-1$.

We recall the definitions of strong convergence in the mean square sense and numerical stability [2]. Let $n_t = \max_{0 \leq n \leq t} n (0 \leq t \leq T)$ and $C > 0$ be a generic constant that may be different at each occurrence.

Definition 2.1. A discrete time approximation Y_n converges with strong order $\gamma > 0$ in the mean square sense if there exist constants Δ and C, not depending on Δ, such that

$$\max_{0 \leq n \leq N} \left(E \parallel X(t_n) - Y_n \parallel^2\right)^{1/2} \leq C\Delta^{\gamma}.$$

Definition 2.2. Let Y denote a time discrete approximation (i.e., numerical solution) with a time-step size $\Delta > 0$ and an initial value Y_0, and let $\widehat{Y}$ denote the corresponding approximation (constructed using the same driving Brownian path) with an initial value $\widehat{Y}_0$. A time discrete Y is called stochastically numerical stable for a given stochastic differential equation if for any finite interval [0,T] there exists a constant Δ_0 such that for $\epsilon > 0$ and $\Delta \in (0, \Delta_0)$

$$\lim_{\|Y_0 - \widehat{Y}_0\| \to 0} \sup_{0 \leq t \leq T} P\left(\parallel Y_{n_t} - \widehat{Y}_{n_t} \parallel \geq \epsilon\right) = 0.$$

3. Convergence in mean square sense

In order to obtain error estimates for the numerical solution Y_{n+1} of (3) , we introduce another variable $Y_{n+1}^{t_n}$ for calculating the error $E\| \left(X(t_{n+1}) - Y_{n+1}^{t_n}\right) + \left(Y_{n+1}^{t_n} - Y_{n+1}\right) \|^2$. Here the variable $Y_{n+1}^{t_n}$ denotes the solution of the numerical scheme

$$Y_{n+1}^{t_n} = Y_n^{t_n} + a\left(Y_n^{t_n}\right)\Delta + \sum_{j=1}^{m} b_j\left(Y_n^{t_n}\right)\Delta W_j\left(t_n\right) \tag{4}$$

with an initial condition $Y_n^{t_n} = X\left(t_n\right)$. For using the Itô formula related with the time-discrete approximation $Y_{n+1}^{t_n}$, we define the time-continuous approximation $Y_t^{t_n} = (Y_{t,1}^{t_n}, \cdots, Y_{t,5}^{t_n})$ as the solution of the scheme for $t_n \leq t \leq t_{n+1}$,

$$Y_t^{t_n} = Y_n^{t_n} + a\left(Y_n^{t_n}\right)(t - t_n) + \sum_{j=1}^{m} b_j\left(Y_n^{t_n}\right)\left(W_j\left(t\right) - W_j\left(t_n\right)\right). \tag{5}$$

Note that $Y_t^{t_n} = Y_n^{t_n}$ at $t = t_n$ and $Y_t^{t_n} = Y_{n+1}^{t_n}$ at $t = t_{n+1}$.

The following lemmas are needed to prove the main theorem in this section.

Lemma 3.1. *Let $X\left(t\right)$, Y_{n+1} and $Y_t^{t_n}$ be the solutions for* (2)*,* (3) *and* (5)*, respectively. Then there exists a constant C such that for $n = 0, \cdots, N-1$ and $0 \leq t \leq T$,*

$$E\left\|X\left(t\right)\right\|^2 + E\left\|Y_{n+1}\right\|^2 + E\left\|Y_t^{t_n}\right\|^2 \leq C.$$

Proof. Note that from (2) and Itô isometry (see [3]),

$$E\left\|X\left(t\right)\right\|^2 = E\left\|X(0) + \int_0^t a(X(s))ds + \sum_{j=1}^{m}\int_0^t b_j\left(X(s)\right)dW_j(s)\right\|^2 \tag{6}$$

$$\leq C\left(E\|X(0)\|^2 + \int_0^t E\|a(X(s))\|^2 ds + \sum_{j=1}^{m}\int_0^t E\|b_j\left(X(s)\right)\|^2 ds\right).$$

Using the definitions of $a(X(t))$ and $b_j(X(t))$ in (1)-(2), we obtain for some C,

$$\|a(X(t))\|^2 + \|b_j(X(t))\|^2 \leq C\|X(t)\|^2,\ 1 \leq j \leq m, \tag{7}$$

which simplifies (6):

$$E\left\|X\left(t\right)\right\|^2 \leq CE\|X(0)\|^2 + C\int_0^t E\|X(s)\|^2 ds.$$

This inequality implies the existence of a constant C such that

$$E\left\|X\left(t\right)\right\|^2 \leq C \tag{8}$$

by using the Grownwall inequality. The boundedness of the other two expectations can be shown by a similar argument, which completes the proof. □

The Lemma 3.1 means that the solutions of (2)–(5) are bounded in the mean square sense, which is used in proving Lemma 3.2.

Lemma 3.2. *Let $X(t_{n+1})$ and $Y_{n+1}^{t_n}$ be the solutions for (2) and (4), respectively. Then there exists a constant C such that for $n = 0, \cdots, N-1$,*

$$E\left\|X(t_{n+1}) - Y_{n+1}^{t_n}\right\|^2 \le C\Delta^2.$$

Proof. It follows from (2) and (4), and the definition of the Itô stochastic integral that

$$X(t_{n+1}) - Y_{n+1}^{t_n} \tag{9}$$
$$= \int_{t_n}^{t_{n+1}} \left(a\left(X(t)\right) - a\left(X(t_n)\right)\right) dt + \sum_{j=1}^{m} \int_{t_n}^{t_{n+1}} \left(b_j\left(X(t)\right) - b_j\left(X(t_n)\right)\right) dW_j(t),$$

which can be written as

$$d\left(X(t) - Y_t^{t_n}\right) = \left(a\left(X(t)\right) - a\left(X(t_n)\right)\right) dt + \sum_{j=1}^{m} \left(b_j\left(X(t)\right) - b_j\left(X(t_n)\right)\right) dW_j(t)$$
$$\equiv \widetilde{a}(t)dt + \sum_{j=1}^{m} \widetilde{b}_j(t) dW_j(t). \tag{10}$$

The initial condition $X_i(t_n) - Y_{n,i}^{t_n} = 0$ $(1 \le i \le 5)$, the Itô formula with (10) and $f\left(X_i(t) - Y_{t,i}^{t_n}\right) = \left(X_i(t) - Y_{t,i}^{t_n}\right)^2$ imply

$$\left(X_i(t_{n+1}) - Y_{n+1,i}^{t_n}\right)^2 = \int_{t_n}^{t_{n+1}} \left(2\left(X_i(t) - Y_{t,i}^{t_n}\right)\widetilde{a}_i(t) + \sum_{j=1}^{m}\left(\widetilde{b}_{ij}(t)\right)^2\right) dt$$
$$+ \sum_{j=1}^{m} \int_{t_n}^{t_{n+1}} 2\left(X_i(t) - Y_{t,i}^{t_n}\right)\widetilde{b}_{ij}(t) dW_j(t). \tag{11}$$

Taking the expectation in (11), we obtain

$$E\left\|X(t_{n+1}) - Y_{n+1}^{t_n}\right\|^2 = \int_{t_n}^{t_{n+1}} E\left(2\left\langle X(t) - Y_t^{t_n}, \widetilde{a}(t)\right\rangle + \sum_{j=1}^{m}\left\|\widetilde{b}_j(t)\right\|^2\right) dt$$
$$+ \sum_{j=1}^{m} E\int_{t_n}^{t_{n+1}} 2\left\langle X(t) - Y_t^{t_n}, \widetilde{b}_j(t)\right\rangle dW_j(t), \tag{12}$$

where the last term on the right hand side of (12) is equal to zero by using the definition of the Itô stochastic integral and the fact that $\left(X_i(t) - Y_{t,i}^{t_n}\right)\widetilde{b}_{ij}(t)$ and $\Delta W_j(t)$ are independent with $E(W_j(t) - W_j(s)) = 0$. For the calculation of the other terms in (12), note that

$$E\left\|X(t) - Y_t^{t_n}\right\|^2 = \int_{t_n}^{t} E\left(2\left\langle X(s) - Y_s^{t_n}, \widetilde{a}(s)\right\rangle + \sum_{j=1}^{m}\left\|\widetilde{b}_j(s)\right\|^2\right) ds$$

$$\leq C\int_{t_n}^{t} ds \leq C(t-t_n), \tag{13}$$

and

$$\begin{aligned} E\left\|X(t)-X(t_n)\right\|^2 &\leq CE\int_{t_n}^{t}\left\|a(X(s))\right\|^2 ds + C\sum_{j=1}^{m} E\left\|\int_{t_n}^{t} b_j(X(s))dW_j(s)\right\|^2 \\ &= CE\int_{t_n}^{t}\left\|a(X(s))\right\|^2 ds + C\sum_{j=1}^{m} E\int_{t_n}^{t}\left\|b_j(X(s))\right\|^2 ds \\ &\leq C(t-t_n). \end{aligned} \tag{14}$$

The equality in (13) is obtained by replacing $Y_{n+1}^{t_n}$ and t_{n+1} in (12) with $Y_t^{t_n}$ and t, respectively. (7)–(8) imply the inequality in (13). The Itô isometry (see [3]) implies the equality in (14). The last inequality is obtained by using (7)–(8). Note that

$$\left\|\widetilde{a}(t)\right\|^2 + \left\|\widetilde{b}_j(t)\right\|^2 \leq C\left\|X(t)-X(t_n)\right\|^2, \tag{15}$$

which is obtained from the special type of fractions on the right hand side of (1). For example, $\overline{Ras}-[RasGTP] \geq 0$ implies $\frac{\overline{Ras}-[RasGTP]}{K_{mk_1}+\overline{Ras}-[RasGTP]} < 1$. Therefore by using (13)–(15) and Youngs inequality, the equation (12) becomes the desired result. □

Lemma 3.3. *Let $X(t), Y_{n+1}$ and $Y_{n+1}^{t_n}$ be the solutions for (2)–(4), respectively. Then there exists a constant C such that for $n = 0, \cdots, N-1$,*

$$E\left\langle X(t_{n+1})-Y_{n+1}^{t_n}, Y_{n+1}^{t_n}-Y_{n+1}\right\rangle \leq C\Delta\left(\Delta + E\|X(t_n)-Y_n\|^2\right).$$

Proof. The equations (3) and (4) imply

$$\begin{aligned} &E\left\langle X(t_{n+1})-Y_{n+1}^{t_n}, Y_{n+1}^{t_n}-Y_{n+1}\right\rangle \\ &\quad= E\left\langle X(t_{n+1})-Y_{n+1}^{t_n}, X(t_n)-Y_n\right\rangle \\ &\quad+ E\left\langle X(t_{n+1})-Y_{n+1}^{t_n}, \phi(X(t_n))-\phi(Y_n)\right\rangle, \end{aligned} \tag{16}$$

where

$$\phi(Y_n) = a(Y_n)\Delta + \sum_{j=1}^{m} b_j(Y_n)\Delta W_j(t_n). \tag{17}$$

For the calculation of the first term on the right hand side of (16), the conditional expectation is used as follows.

$$\begin{aligned} &E\left\langle X(t_{n+1})-Y_{n+1}^{t_n}, X(t_n)-Y_n\right\rangle \\ &\quad= E\left[E\left(\left\langle X(t_{n+1})-Y_{n+1}^{t_n}, X(t_n)-Y_n\right\rangle \middle| \mathcal{F}_{t_n}\right)\right] \\ &\quad\leq \left(E\left\|E\left(X(t_{n+1})-Y_{n+1}^{t_n} \middle| \mathcal{F}_{t_n}\right)\right\|^2\right)^{1/2}\left(E\|X(t_n)-Y_n\|^2\right)^{1/2}. \end{aligned} \tag{18}$$

The inequality in (18) is obtained by using the $\mathcal{F}_{t_n}$-measurability of $X(t_n) - Y_n$ and the Cauchy Schwarz inequality. It follows from (9), the linearity of the conditional expectation, the triangle inequality, the Jensen inequality (see [3]), the martingale property, (15), and (14) that

$$\begin{aligned}
&E\left\|E\left(X(t_{n+1}) - Y_{n+1}^{t_n}\middle|\mathcal{F}_{t_n}\right)\right\|^2 \\
&\equiv E\left\|E\left[\left(\int_{t_n}^{t_{n+1}} \widetilde{a}(t)dt + \sum_{j=1}^{m}\int_{t_n}^{t_{n+1}} \widetilde{b}_j(t)dW_j(t)\right)\middle|\mathcal{F}_{t_n}\right]\right\|^2 \\
&\leq CE\left\|E\left(\int_{t_n}^{t_{n+1}} \widetilde{a}(t)dt\middle|\mathcal{F}_{t_n}\right)\right\|^2 + CE\left\|E\left(\sum_{j=1}^{m}\int_{t_n}^{t_{n+1}} \widetilde{b}_j(t)dW_j(t)\middle|\mathcal{F}_{t_n}\right)\right\|^2 \\
&= CE\left\|\int_{t_n}^{t_{n+1}} \widetilde{a}(t)dt\right\|^2 \leq CE\left(\Delta\int_{t_n}^{t_{n+1}} \|\widetilde{a}(t)\|^2 dt\right) \leq C\Delta\int_{t_n}^{t_{n+1}} (t - t_n)\,dt \\
&\leq C\Delta^3.
\end{aligned} \tag{19}$$

Letting $\varepsilon_n^2 = E\|X(t_n) - Y_n\|^2$ and substituting (19) into (18), we obtain

$$E\left\langle X(t_{n+1}) - Y_{n+1}^{t_n}, X(t_n) - Y_n\right\rangle \leq C\Delta\left(\Delta + \varepsilon_n^2\right). \tag{20}$$

Apply (17) and (19) to the last term in (16) for obtaining the upper bound

$$\begin{aligned}
&E\left\langle X(t_{n+1}) - Y_{n+1}^{t_n}, \phi(X(t_n)) - \phi(Y_n)\right\rangle \\
&\quad\equiv E\left\langle X(t_{n+1}) - Y_{n+1}^{t_n}, \widehat{a}(t)\Delta + \sum_{j=1}^{m}\widehat{b}_j(t)\Delta W_j(t_n)\right\rangle \\
&\quad\leq C\Delta^{\frac{3}{2}}\left(E\left\|\widehat{a}(t)\Delta + \sum_{j=1}^{m}\widehat{b}_j(t)\Delta W_j(t_n)\right\|^2\right)^{1/2}.
\end{aligned} \tag{21}$$

By using the distribution of $\Delta W_j(t_n)$ and the independence of $X(t_n) - Y_n$ and $\Delta W_j(t_n)$, the last term in (21) becomes

$$E\left\|\widehat{a}(t)\Delta + \sum_{j=1}^{m}\widehat{b}_j(t)\Delta W_j(t_n)\right\|^2 \leq C\Delta \cdot E\|\widehat{a}(t)\|^2 \leq C\Delta\cdot\varepsilon_n^2, \tag{22}$$

which implies, by using Youngs inequality,

$$E\left\langle X(t_{n+1}) - Y_{n+1}^{t_n}, \phi(X(t_n)) - \phi(Y_n)\right\rangle \leq C\Delta\left(\Delta + E\|X(t_n) - Y_n\|^2\right). \tag{23}$$

Substituting (20) and (23) into (16), we obtain the desired result. □

Lemma 3.4. *Let $X(t), Y_{n+1}$ and $Y_{n+1}^{t_n}$ be the solutions for* (2)–(4)*, respectively. Then there exists a constant C such that for $n = 0, \cdots, N-1$,*

$$E\|Y_{n+1}^{t_n} - Y_{n+1}\|^2 \le (1 + C\Delta)\, E\|X(t_n) - Y_n\|^2.$$

Proof. For simplicity, define the notations $\breve{a}(t_n)$ and $\breve{b}_j(t_n)$ to satisfy

$$Y_{n+1}^{t_n} - Y_{n+1} = X(t_n) - Y_n + \breve{a}(t_n)\Delta + \sum_{j=1}^{m} \breve{b}_j(t_n)\Delta W_j(t_n). \tag{24}$$

Taking the norm and the expectation of the both sides of (24), we obtain

$$E\left\|Y_{n+1}^{t_n} - Y_{n+1}\right\|^2 = \varepsilon_n^2 + 2E\left\langle X(t_n) - Y_n, \breve{a}(t_n)\Delta + \sum_{j=1}^{m} \breve{b}_j(t_n)\Delta W_j(t_n)\right\rangle + E\left\|\breve{a}(t_n)\Delta + \sum_{j=1}^{m} \breve{b}_j(t_n)\Delta W_j(t_n)\right\|^2. \tag{25}$$

The second term on the right hand side of (25) can be written as

$$\begin{aligned} &E\left\langle X(t_n) - Y_n, \breve{a}(t_n)\Delta + \sum_{j=1}^{m} \breve{b}_j(t_n)\Delta W_j(t_n)\right\rangle \\ &= E\left[E\left(\left\langle X(t_n) - Y_n, \breve{a}(t_n)\Delta + \sum_{j=1}^{m} \breve{b}_j(t_n)\Delta W_j(t_n)\right\rangle \middle| \mathcal{F}_{t_n}\right)\right] \\ &= E\left\langle X(t_n) - Y_n, \breve{a}(t_n)\Delta + E\left(\sum_{j=1}^{m} \breve{b}_j(t_n)\Delta W_j(t_n) \middle| \mathcal{F}_{t_n}\right)\right\rangle \\ &= E\langle X(t_n) - Y_n, \breve{a}(t_n)\Delta\rangle \le C\Delta \cdot \varepsilon_n^2, \end{aligned}$$

where the last equality is obtained by using the fact that $X(t_n) - Y_n, \breve{a}(t_n), \breve{b}_j(t_n)$ are $\mathcal{F}_{t_n}$-measurable and $\Delta W_j(t_n)$ are independent of $\mathcal{F}_{t_n}$. We use CauchySchwarz inequality and $Y_n^{t_n} = X(t_n)$ with (15) to obtain the last inequality.
Since $X(t_n)$ and Y_n are independent of $\Delta W_j(t_n)$, the last term on the right hand side of (25) becomes

$$\begin{aligned} &E\left\|\breve{a}(t_n)\Delta + \sum_{j=1}^{m} \breve{b}_j(t_n)\Delta W_j(t_n)\right\|^2 \\ &\qquad \le C\Delta \cdot E\left\|\breve{a}(t_n)\right\|^2 + C\sum_{j=1}^{m} E\left\|\breve{b}_j(t_n)\right\|^2 \cdot E\left(\Delta W_j(t_n)\right)^2 \\ &\qquad \le C\Delta \cdot \varepsilon_n^2. \end{aligned}$$

Therefore the proof is completed. □

Using Lemma 3.1–Lemma 3.4, we obtain the following error estimation.

Theorem 3.5. *Let $X(t)$ and Y_n be the solutions for* (2)–(3)*, respectively. Then there exists a constant C such that*

$$\max_{0\le n\le N} E\|X(t_n)-Y_n\|^2 \le C\Delta.$$

Proof. Simple algebra yields

$$\begin{aligned}\|X(t_{n+1})-Y_{n+1}\|^2 &= \|X(t_{n+1})-Y_{n+1}^{t_n}\|^2\\ &+ 2\langle X(t_{n+1})-Y_{n+1}^{t_n}, Y_{n+1}^{t_n}-Y_{n+1}\rangle + \|Y_{n+1}^{t_n}-Y_{n+1}\|^2.\end{aligned}$$

After taking the expectation and using Lemma 3.2–Lemma 3.4, we obtain

$$\begin{aligned}&E\|X(t_{n+1})-Y_{n+1}\|^2\\ &\quad= E\|X(t_{n+1})-Y_{n+1}^{t_n}\|^2\\ &\qquad+2E\left\langle X(t_{n+1})-Y_{n+1}^{t_n}, Y_{n+1}^{t_n}-Y_{n+1}\right\rangle + E\|Y_{n+1}^{t_n}-Y_{n+1}\|^2\\ &\quad\le E\|X(t_n)-Y_n\|^2(1+C\Delta)+C\Delta^2.\end{aligned}$$

Therefore the proof is completed by applying the Grownwall inequality. □

4. Numerical stability

In order to consider the stability of the numerical solution Y_n of (3) with the Definition 2, let $\widehat{Y}_{n+1}$ be the corresponding solution for the equation

$$\widehat{Y}_{n+1} = \widehat{Y}_n + a\left(\widehat{Y}_n\right)\Delta + \sum_{j=1}^{m} b_j\left(\widehat{Y}_n\right)\Delta W_j(t_n). \tag{26}$$

The following theorem is the stochastically numerical stability of the solution Y_n.

Theorem 4.1. *Let Y_{n+1} and $\widehat{Y}_{n+1}$ be the solutions for* (3) *and* (26)*, respectively. Then there exists a constant Δ_0 such that for $\epsilon > 0$ and $\Delta \in (0,\Delta_0)$*

$$\lim_{\left\|Y_0-\widehat{Y}_0\right\|\to 0}\ \sup_{0\le t\le T} P\left(\left\|Y_{n_t}-\widehat{Y}_{n_t}\right\|\ge\epsilon\right)=0.$$

Proof. The Chebyshev inequality implies for $\epsilon > 0$,

$$P\left(\left\|Y_{n_t}-\widehat{Y}_{n_t}\right\|\ge\epsilon\right)\le\frac{E\left(\left\|Y_{n_t}-\widehat{Y}_{n_t}\right\|^2\right)}{\epsilon^2}.$$

Letting $D(t)=\sup_{0\le s\le t} E\left(\left\|Y_{n_s}-\widehat{Y}_{n_t}\right\|^2\right)$, we will show

$$D(t)\le CE\left\|Y_0-\widehat{Y}_0\right\|^2 + C\int_0^t D(t)\,dt, \tag{27}$$

which completes the proof by using the Grownwall inequality: When $\left\|Y_0 - \widehat{Y}_0\right\| \to 0$,

$$P\left(\left\|Y_{n_t} - \widehat{Y}_{n_t}\right\| \geq \epsilon\right) \leq \frac{E\left(\left\|Y_{n_t} - \widehat{Y}_{n_t}\right\|^2\right)}{\epsilon^2} \leq \frac{D\,(T)}{\epsilon^2} \leq CE\left(\left\|Y_0 - \widehat{Y}_0\right\|^2\right) \to 0.$$

Define ϕ_n and $\widehat{\phi}_n$ to satisfy both $Y_{n+1} = Y_n + \phi_n$ and $\widehat{Y}_{n+1} = \widehat{Y}_n + \widehat{\phi}_n$. Then

$$\begin{aligned}
&E\left(\left\|Y_{n_s} - \widehat{Y}_{n_s}\right\|^2\right) \\
&= E\Bigg(\bigg\|Y_0 - \widehat{Y}_0 + \sum_{n=0}^{n_s-1} E\Big(\left(\phi_n - \widehat{\phi}_n\right)\Big|\,\mathcal{F}_{t_n}\Big) \\
&\qquad + \sum_{n=0}^{n_s-1}\left\{\phi_n - \widehat{\phi}_n - E\left(\left(\phi_n - \widehat{\phi}_n\right)\Big|\,\mathcal{F}_{t_n}\right)\right\}\bigg\|^2\Bigg) \\
&\leq CE\left\|Y_0 - \widehat{Y}_0\right\|^2 + CE\left\|\sum_{n=0}^{n_s-1} E\left(\left(\phi_n - \widehat{\phi}_n\right)\Big|\,\mathcal{F}_{t_n}\right)\right\|^2 \\
&\qquad + CE\left\|\sum_{n=0}^{n_s-1}\left\{\phi_n - \widehat{\phi}_n - E\left(\left(\phi_n - \widehat{\phi}_n\right)\Big|\,\mathcal{F}_{t_n}\right)\right\}\right\|^2. \qquad (28)
\end{aligned}$$

Apply the idea used to obtain (15) and (19) for finding the upper bound of the last second term in (28)

$$\begin{aligned}
E\left\|\sum_{n=0}^{n_s-1} E\left(\left(\phi_n - \widehat{\phi}_n\right)\Big|\,\mathcal{F}_{t_n}\right)\right\|^2 &\leq C\sum_{n=0}^{n_s-1} E\left(\left\|Y_n - \widehat{Y}_n\right\|^2\right)\cdot\Delta \\
&\leq C\int_0^t D(t)\;dt. \qquad (29)
\end{aligned}$$

For the last term in (28), note that for $i > j$

$$\begin{aligned}
&E\left\langle \phi_i - \widehat{\phi}_i - E\left(\left(\phi_i - \widehat{\phi}_i\right)\Big|\,\mathcal{F}_{t_i}\right)\;,\;\phi_j - \widehat{\phi}_j - E\left(\left(\phi_j - \widehat{\phi}_j\right)\Big|\,\mathcal{F}_{t_j}\right)\right\rangle \\
&= E\left[E\left\{\left\langle \phi_i - \widehat{\phi}_i - E\left(\left(\phi_i - \widehat{\phi}_i\right)\Big|\,\mathcal{F}_{t_i}\right)\;,\;\phi_j - \widehat{\phi}_j - E\left(\left(\phi_j - \widehat{\phi}_j\right)\Big|\,\mathcal{F}_{t_j}\right)\right\rangle\Big|\,\mathcal{F}_{t_i}\right\}\right] \\
&= E\left\langle E\left[\left\{\phi_i - \widehat{\phi}_i - E\left(\left(\phi_i - \widehat{\phi}_i\right)\Big|\,\mathcal{F}_{t_i}\right)\right\}\Big|\,\mathcal{F}_{t_i}\right]\;,\;\phi_j - \widehat{\phi}_j - E\left(\left(\phi_j - \widehat{\phi}_j\right)\Big|\,\mathcal{F}_{t_j}\right)\right\rangle \\
&= E\left\langle 0\;,\;\phi_j - \widehat{\phi}_j - E\left(\left(\phi_j - \widehat{\phi}_j\right)\Big|\,\mathcal{F}_{t_j}\right)\right\rangle = 0, \qquad (30)
\end{aligned}$$

where the first and second equalities are obtained by using the definition of conditional expectation and the fact that ΔW_j is independent of $\mathcal{F}_{t_i}$ and $Y_i, Y_j, \widehat{Y}_i, \widehat{Y}_j$, $E\left(\left(\phi_j - \widehat{\phi}_j\right)\Big|\,\mathcal{F}_{t_j}\right)$ are $\mathcal{F}_{t_i}$-measurable. For the third equality in (30), we use the $\mathcal{F}_{t_i}$-measurability of $E\left(\left(\phi_i - \widehat{\phi}_i\right)\Big|\,\mathcal{F}_{t_i}\right)$. The equation (30) and the Jensen inequality imply that the upper bound of the last term in (28) is of the form

$$\begin{aligned} E\left\|\sum_{n=0}^{n_s-1}\left\{\phi_n - \widehat{\phi}_n - E\left(\left(\phi_n - \widehat{\phi}_n\right)\Big|\,\mathcal{F}_{t_n}\right)\right\}\right\|^2 \\ &= \sum_{n=0}^{n_s-1} E\left\|\phi_n - \widehat{\phi}_n - E\left(\left(\phi_n - \widehat{\phi}_n\right)\Big|\,\mathcal{F}_{t_n}\right)\right\|^2 \\ &\le C\sum_{n=0}^{n_s-1}\left(E\left\|\phi_n - \widehat{\phi}_n\right\|^2 + E\left[E\left(\left\|\phi_n - \widehat{\phi}_n\right\|^2\Big|\,\mathcal{F}_{t_n}\right)\right]\right) \\ &\le C\sum_{n=0}^{n_s-1} E\left\|\phi_n - \widehat{\phi}_n\right\|^2 \le C\int_0^t D(t)\,dt. \end{aligned} \tag{31}$$

Substituting (29) and (31) into (28), we obtain (27). □

Remark 4.1. The stable numerical scheme (3) will be used to show the impact of intrinsic noise on the system dynamics for future study. Incorporation of stochasticity into other deterministic models (see [1]) and theoretical analysis on positivity of the solutions will be also studied in the future.

References

1. S.M. Choo, *Finite difference schemes for calcium diffusion equations*, J. Appl. Math. Informatics **26**(2008), 299 - 306.
2. P.E. Kloeden and E. Platen, *Numerical Solution of Stochastic Differential Equations*, Springer-Verlag, New York, 1988.
3. B. Oksendal, *Stochastic Differential Equations*, 6th ed. Springer, New York, 2010.
4. S.Y. Shin, O. Rath, S.M. Choo, F. Fee, B. McFerran, W. Kolch, and K.H. Cho, *Positive- and negative-feedback regulations coordinate the dynamic behavior of the Ras-Raf-MEK-ERK signal transduction pathway*, J Cell Sci. **122**(2009), 425-435.

S.M. Choo received his degrees of B.S. and M.S. from Seoul National University. He earned his Ph.D. at Seoul National University under the direction of S.K. Chung. He has been at University of Ulsan since September, 2001. His research interest are numerical analysis, systems biology and stochastic processes.

Department of Mathematics, University of Ulsan, Ulsan 680–749, Korea.
e-mail: smchoo@ulsan.ac.kr

Y.H. Kim received her degrees of B.S. and M.S. from Yonsei University. She earned her Ph.D. at Yonsei University under the direction of M.S. Song. She has been at Kwangwoon University since September, 2003. Her reserch interests are numerical analysis, biological mathematics and p-adic analysis.

Division of General Education, Kwangwoon University Seoul 137-701, Korea.
e-mail: yhkim@kw.ac.kr