Euler-Maruyama Approximation and Maximum Likelihood Estimator for a Stochastic Differential Equation Model of the Signal Transduction Process

Din Prathumwan, Yongwimon Lenbury, Pairote Satiracoo, Chontita Rattanakul

***Abstract*—**The conversion of an external signal by the cell into internal molecules is called the signal transduction process. In this paper, the role of the G-protein coupled receptors (GPCRs) is considered because GPCRs constitute the largest family of protein on eukaryotic cell membrane. Furthermore, GPCRs can detect the external signals and transduce them into the cell leading to the production of the secondary hormone or massager such as cAMP (cyclic adenosine monophosphate). The abnormality of the signal transduction process can cause many serious diseases. Better understanding of GPCRs and the signal transduction process should be greatly beneficial for pharmacological research. Here, a stochastic differential equation (SDE) model of the signal transduction in the cell has been proposed and investigated. An SDE model has been modified from the deterministic model proposed by Rattanakul et al. (2009) to take into account the observation that experimental data on cAMP measurements often show random fluctuations (Ueda and Shibata, 2007). The model parameters are then estimated by using the Euler-Maruyama approximation and maximum likelihood estimators. With the estimated parameters, the stochastic model simulations are found to provide a better dynamic representation of the transduction system with noise, in comparison to the deterministic model which does not take into account the random fluctuations in the production of the secondary signaling hormone, cAMP, which could significantly impact the amplification effect that it has on the primary signaling hormone. Such stochastic behavior can significantly influence the outcome of the process which controls the proper function of the human body. We discuss the simulation results of the SDE model with estimated parametric values in comparison with those obtained from the deterministic model proposed by Ratanakul et al. [80], with parameter values estimated by a genetic algorithm.

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I. Introduction

A cell is the smallest unit of the living organism. Organism is composed of cells which are unicellular (a single cell) or multicellular. A regular cell size is 10 micron and a regular mass is 1 nanogram. The cells need to communicate with each other in order to perform their functions which are growth, creation, metabolism, and so on. The cell can sense and respond to other cells or surrounding signals through a signaling process [1].

Normally, the signaling process involves extracellular signaling molecules and receptors on cell membrane. The cell membrane has many receptors, one of the largest family of which is that of G-protein-coupled receptors (GPCRs).

GPCRs which are found only in eukaryotic cells control every aspect in pathological processes. The signaling process consists of three stages; signal reception, transduction, and response. First, the receptors detect the chemical signal from the environment. When the chemical signal binds to the receptors, the signal transduction turns the exterior stimuli into a form which can produce an exact cellular response. Lastly, the transduced signal triggers an exact cellular response. After all these processes have occurred, the signaling process must be terminated [2].

The common feature in all signal transduction pathways is that a component in the environment is recognized, typically by a protein in the plasma membrane. The environmental trigger is called the ligand, and the plasma membrane protein is called the receptor. The receptor usually spans the membrane, and binding to the ligand on the extracellular side triggers a change that activates its function on the intracellular side. This part of the process is called signal transduction [3].

Any abnormalities in the signal transduction process can

cause many serious diseases, such as diabetes and cancer, which arises from a cell that cannot respond to the signal properly. For example, a signaling process which fails to suitably terminate can cause uncontrolled cell activities such as abnormal growth and the possibility of cancer. For this reason, in depth understanding of the signal transduction process is crucial for pharmacological research and effective drug development [2], [3], [4].

In a previous work, Levchenko and Iglesias [5] proposed a model for the chemotactic signaling system which explains the conversion of a shallow gradient of chemo attractant in Dictyostelium and neutrophils. They found that local excitation and global inhibition are controlled by the G protein activation.

In 2003, Iglesias [6] proposed a deterministic model for the signaling process associated with chemotaxis in Dictyostelium which is based on gradient sensing and adaptation. The model considers both the positive feedback loop and the negative feedback loops. His paper discusses how control engineering mechanisms such as robustness and amplification are similar to those found in the signal transduction pathways.

In 2006, based on the model proposed by Iglesias, Rattanakul et al. [7] invistigated a deterministic model of signal transduction pathway, which involves the G protein coupled receptors, consisting of a system of two differential equations governing the interaction between the inhibitor protein and the ligand – receptor complexes. Signal transduction across the plasma membrane is mediated by membrane receptor bound proteins which connect the genetically controlled biochemical reactions in the cytosol to the production of the second messenger, leading to desired intracellular responses. Their model took into account the receptors internalization and incorporated receptor diffusion and movement across the cell membrane.

On considering the experimental data reported by Rattankul et al. in [8], it was observed that the cAMP level fluctuates randomly. According to Felber et al. [9], who proposed the master equation simulation of the underlying diffusional effect involving the G-protein, the diffusion and reaction showed probabilistic nature and behave in stochastic fashion. They calculated the kinetics of the active effector from signaling process which is determined by the stochastic lifetime distribution.

In an earlier work by Oosawa [10], it was proposed that a fluctuation in the signal is generated by thermal fluctuations of biomolecules. Oosawa constructed a theory to describe the mechanism of signal generation [10]. Also, Lamb [11] presented the simulation results for the two-dimensional diffusional interactions involving the protein receptors and the stochastic simulations confirmed a simplified analytic model which he proposed. The simulation also gave the efficiency quantitative estimates of coupling in the concentration of activated G-protein to activated effector.

More recently, Ueda and Shibata [12] proposed a stochastic model of chemotactic signaling by which noise and signal propagation along the transmembrane signaling pathway by chemoattractant receptors can be analyzed quantitatively. They found that an extrinsic noise could occur when ligands stochastically bind to receptors and intrinsic noise which arises when the receptors generate noisy second messengers.

The work of Naoki et al. [13] reveals that information of external signal is amplified using the frequencies of intracellular noise. The stochastic reactions allow the system to spontaneously become excited and the performance of cell is improved by this effect.

Taking into account such observations mentioned above, it appears that many researchers have discovered and investigated the occurrences of fluctuation in biomolecules. This agrees with the data on experimental measurements of cAMP reported by Rattanakul et al. [8] which exhibited noisy fluctuation in the cAMP level. We will therefore construct a stochastic differential equation model that will describe more accurately the dynamic behavior of the system. Modified from the deterministic model proposed by Rattanakul et al. [8], the SDE model takes into account the impact of random fluctuations in the amplification effects of the secondary hormone on the first signal from the external environment of the cell. Then, the model parameters are estimated by using the Euler - Maruyama approximation and Maximum likelihood estimator.

II. The Transduction Process

Cells have a mechanism for detecting and responding to external signals. One of the more complex tactics for doing this involves a three-stage G protein coupled enzyme cascade [2], a schematic diagram of which is shown in Figure 3.

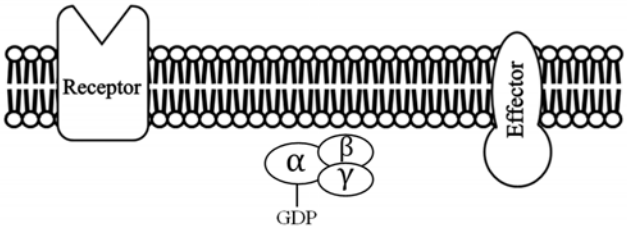

Fig. 1 The basal level of G-protein GTPase cycle.

In the first stage, the basal stage, the G protein which is constituted of 3 subunits: α, β and γ subunits, with GDP bound to the α - subunit, is activated by the receptor's interaction with a particular ligand.

In the second stage, the transduction stage, after the receptor has been activated and turned on the heterotrimeric G protein,

by causing the G protein to replace GDP (guanosine diphosphate) by GTP (guanosine triphosphate), the GTP-bound α - subunit then dissociates from β and γ subunits and either or both regulates the effector unit whose activity produces secondary messengers, such as cyclic adenosine monophosphate (cAMP).

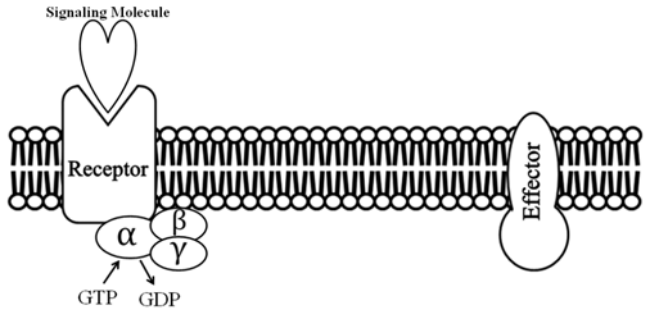

Fig. 2 The activation of α-subunit of G-protein of G-protein GTPase cycle.

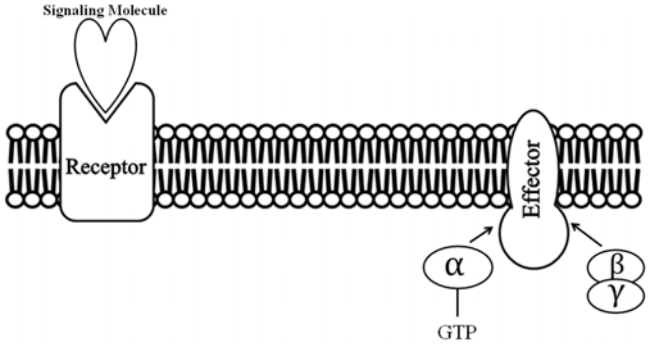

Fig. 3 The activation of effector of G-protein GTPase cycle.

The G protein subunit is transient and it is terminated by the GTPase activity of the α - subunit. GTPase converts bound GTP to GDP then the protein becomes inactivated.

III. The Governing Equations

A. Deterministic model

We could think of the intracellular signal transduction in this way. Adenylyl cyclase (AC) occurs in two stages: active (R^*) and inactive (R). R is converted into R^* by a GDP bound α - subunit of G protein denoted by A and R^* is converted into R by GDP bound α - subunit whose amount is given by I. Moreover, A and I are activated by the external signal which binds to the cell receptors on the cell membrane, becoming G protein coupled receptors at a concentration S. Lastly, the activation of AC leads to the synthesis of cAMP (C) which regulates a downstream reaction to amplify the initial signal.

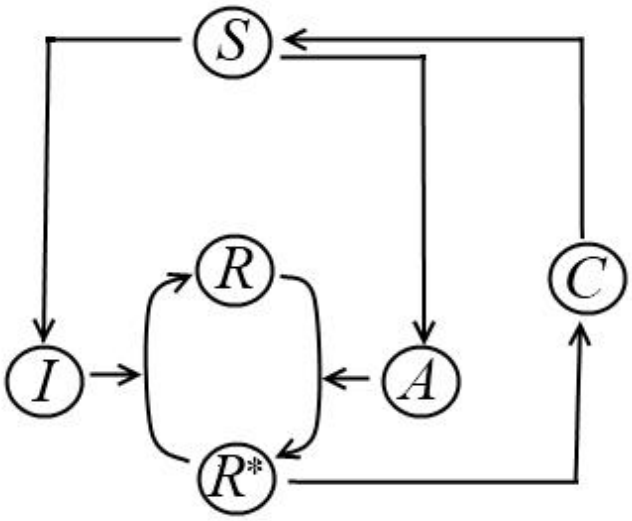

Fig. 4 The reaction scheme of signal transduction involving G-protein coupled receptors.

Based on earlier research works [7, 8, 14], we could consider the above dynamics in the following way.

The equation for R^* can be written as

$$\frac{dR^*}{dt} = -k_{-r} I R^* + k_r A R \tag{1}$$

where the first term on the right is the removal rate and the last term is the activation rate.

Assuming that the total amount of AC is constant denoted by R_T so that $R_T = R^* + R$, Equation (1) becomes

$$\frac{dR^*}{dt} = -(k_{-r} I + k_r A) R^* + k_r A R_T \tag{2}$$

From the scheme seen in Figure 4, the dynamics of the activator of density A and inhibitor of density I are described by the following equations:

$$\frac{dA}{dt} = -k_{-a} A + k_a S \tag{3}$$

and

$$\frac{dI}{dt} = -k_{-i} I + k_i A \tag{4}$$

where the first terms on the right are the corresponding removal rates and the last terms are the corresponding rates of production.

The concentration of the second messenger or cAMP (C) which is synthesized as a result of enzyme R^* activation [15], satisfies the following equation

$$\frac{dC}{dt} = -k_{-c}C + k_{c1}\left[R^*\right]^2 + k_{c2} \tag{5}$$

where the first term on the right is the removal rate and the last two terms represent the synthesis rate, k_{c2} being the zero order rate of production.

The dynamics of S follows the equation

$$\frac{dS}{dt} = -k_{-s}S - \frac{b_1 S}{b_2 + S} + k_s C \tag{6}$$

where the first term on the right is the removal rate, the second term is the rate at which it is internalized through the cell membrane and the last term represents the signal amplification due to the secondary hormone C.

As argued in [5] and [6], we may assume that the dynamics of R^*, A and C are relatively fast compared to the dynamics of I and S. Then, the values of R^*, A and C equilibrate quickly to

$$R^* = \frac{k_r A R_T}{k_{-r} I + k_r A} \tag{7}$$

$$A = \frac{k_s}{k_a} S \tag{8}$$

$$C = \frac{k_{c1}}{k_{-c}}\left[R^*\right]^2 + \frac{k_{c2}}{k_{-c}}. \tag{9}$$

Substituting (8) in (4), we obtain

$$\frac{dI}{dt} = -a_1 I + a_2 S. \tag{10}$$

where

$$a_1 = k_{-i}$$

and

$$a_2 = \frac{k_a k_{-i}}{k_{-a}}.$$

Substituting (7), (8), and (9) in (6), we have

$$\frac{dS}{dt} = -a_3 S - \frac{b_1 S}{b_2 + S} + \frac{a_4 S^2}{(a_5 S + I)^2} + a_6 \tag{11}$$

where

$$a_3 = k_{-s},$$

$$a_4 = \frac{k_{c1} k_s}{k_{-c}}\left(\frac{k_a k_r}{k_{-a} k_{-r}} R_T\right)^2,$$

$$a_5 = \frac{k_a k_r}{k_{-a} k_{-r}},$$

$$a_6 = \frac{k_{c2} k_s}{k_{-c}}.$$

B. B. Formulation of the gradient-sensing SDEs model

Following observations made by researchers mentioned earlier [10 – 13, 16], we could think about the above system (10) - (11) in the following way.

Substituting Equation (7) in (9), one obtains

$$C = k\left[\frac{a_4 S^2}{\left(a_5 S + I\right)^2} + a_6\right] \tag{12}$$

where

$$k = \frac{1}{k_s}.$$

Then, we can write (11) as

$$\frac{dS}{dt} = -a_3 S - \frac{b_1 S}{b_2 + S} + \frac{C}{k}, \quad S(0) = S_0 \tag{13}$$

when C is considered to be erratic.

We hypothesize that C is perturbed by a Gaussian white noise ξ,

$$C \to C + \tilde{\sigma}\xi$$

where $\tilde{\sigma}$ is a positive unknown parameter representing the noise intensity factor.

Then, we obtain

$$\frac{dS}{dt} = -a_3 S - \frac{b_1 S}{b_2 + S} + \frac{C + \tilde{\sigma}\xi}{k} \tag{14}$$

Substituting $\tilde{\sigma}/k$ with σ, one has

$$dS = \left(-a_3 S - \frac{b_1 S}{b_2 + S} + \frac{C}{k}\right)dt + \sigma dW \tag{15}$$

or

$$dS = \left(-a_3 S - \frac{b_1 S}{b_2 + S} + \frac{a_4 S^2}{\left(a_5 S + I\right)^2} + a_6 \right) dt + \sigma dW \tag{16}$$

where W represents a standard Brownian motion.

Therefore, we arrive at the model consisting of the following equations

$$\frac{dI}{dt} = -a_1 I + a_2 S, \quad I(0) = I_0, \tag{17}$$

$$dS = \left(-a_3 S - \frac{b_1 S}{b_2 + S} + \frac{a_4 S^2}{\left(a_5 S + I\right)^2} + a_6 \right) dt + \sigma dW, \quad S(0) = S_0 \tag{18}$$

$$C = k\left[\frac{a_4 S^2}{\left(a_5 S + I\right)^2} + a_6 \right] \tag{19}$$

IV. Parameter Estimations

A. Experimental data

In order to determine whether the above system (17) - (19) gives a suitable model for the transduction process, measurements of intracellular cAMP has been utilized to arrive at estimates for the model parameters. The measurements was done by using Fisher rat thyroid cells stably expressing type II antidiuretic hormone receptors, FRT-V2R, cultured in F-12 modified Coon's medium (Sigma) supplemented with 10% fetal bovine serum, 100 U/ml penicillin and 100 μg/ml streptomycin at 37 $^{\circ}C$ in a humidified atmosphere of 5% CO_2.

Every two weeks, the FRT-V2R cells were selected with medium containing 500 μg/ml Zeocin, 500 μg/ml Geneticin and 350 μg/ml hygromycin. Then, the FRT-V2R cells were plated in 24-well plates overnight. After obtaining 80 % of confluence, the cells were washed three times with PBS and incubated with 100 nM dDAVP (Sigma-Aldrich), a selective V2R agonist.

The incubation time was varied from 5 seconds to 16 minutes. The reaction was terminated by lysis buffer. After the incubation, cell lysate was transferred to 96-well plates. Then, the intracellular cAMP measurement using cAMP Biotrak EIA system (Amersham, GE Healthcare). The measurement protocol follows manufacturer's instructions, and samples were determined at optical density 450 nm [8].

Lowry method (1951) [17] was used to determine the amount of intracellular cAMP expressed per unit amount of protein.

To estimate the parameter values, we consider that the unknown model parameters

$$\left(\theta = \left[a_1, a_2, a_3, a_4, a_5, a_6, b_1, b_2, \sigma\right]\right)$$

could be estimated given the 2 equations. We use Euler-Maruyama approximation and Maximum likelihood estimator [18] to estimate the parameters upon the measured experimental data described above.

B. Euler-Maruyama approximation

Next, we consider the following Itô SDE [19]

$$dX_t = f\left(X_t, \theta\right) dt + g\left(X_t, \theta\right) dW_t \tag{20}$$

$$X(0) = X_0$$

where W is an m - dimensional standard Wiener process and

$$f: \mathbb{R} \times \Theta \to \mathbb{R} \qquad \text{and} \qquad g: \mathbb{R} \times \Theta \to \mathbb{R}^{1 \times m}$$

are known functions depending on an unknown finite-dimensional parameter vector $\theta \in \Theta$.

Considering the Itô SDE (20) on $\left[t_0, T\right]$, for a given discretization $t_o < t_1 < \cdots < t_n < \cdots < t_N = T$ of $\left[t_0, T\right]$, an Euler - Maruyama approximation is a continuous time stochastic process satisfying the iterative scheme

$$\begin{aligned} Y_{n+1} &= Y_n + h_n f\left(Y_n\right) + g\left(Y_n\right) \Delta W_n, \\ Y_0 &= X_0, \quad n = 0, 1, \ldots, N-1 \end{aligned} \tag{21}$$

where

$$\begin{aligned} Y_n &= Y\left(t_n\right), \\ h_n &= t_{n+1} - t_n \text{ is the } \textit{stepsize}, \\ \Delta W_n &= W\left(t_{n+1}\right) - W\left(t_n\right) \sim \boldsymbol{N}\left(0, h_n\right) \end{aligned}$$

with $W\left(t_0\right) = 0$ and $\boldsymbol{N}$ is the normal distribution.

C. Maximum likelihood estimator

The maximum likelihood estimator (MLE) of θ can be calculated if the transition densities $p(x_t; x_s, \theta)$ of X are knows, $s < t$. The log-likelihood function of θ is given by

$$l_n\left(\theta\right) = \sum_{i=1}^{n} \log p\left(x_i, x_{i-1}, \theta\right) \tag{22}$$

and the maximum likelihood estimator $\hat{\theta}$ can be found by maximizing (22) with respect to θ. Under mild regularity

conditions, $\hat{\theta}$ is consistent, asymptotically normally distributed and asymptotically efficient as n tends to infinity.

V. Results and Discussion

The estimated parameter values can be found as given in Table I.

TABLE I

ESTIMATED MODEL PARAMETERS
ON FIRST RUN

parameter	estimated value
a_1	0.90817 ± 0.03345
a_2	0.29170 ± 0.01829
a_3	2.14885 ± 9.38365
a_4	0.06629 ± 0.28644
a_5	0.31687 ± 0.88463
a_6	0.07902 ± 0.24257
b_1	0.31918 ± 2.49458
b_2	0.11690 ± 0.30378
σ	0.00954 ± 0.00249

Simulation results of the identified model are shown in Figure 5 and Figure 6.

We observe that the estimations are reasonable, except possibly for a_3 and b_1 for which the error intervals are relatively large. This is probably because of the limitation on the data set, containing only 13 samples, while we try to estimate 9 parameters.

To check for the consistency of the estimations, a second run was carried out with over 50 simulations. The estimated parameter values are as given in Table II. The parameter estimates are close to the corresponding values in the first run. We still have a large error in the estimate for a_3.

The plots of empirical mean, confidence interval and Q_1 and Q_3 quartiles of the identified model, using the parameter estimates in Table II, are shown in Figure 7, showing wider 95% confidence interval and , while the errors in the estimated parameter values are smaller.

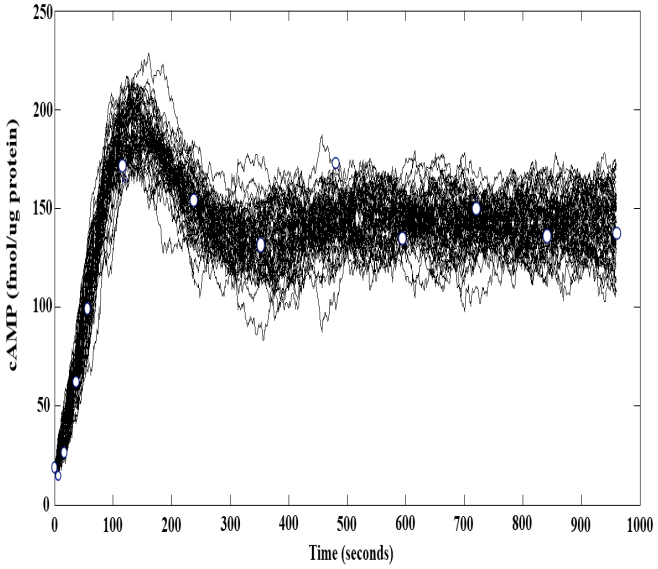

Fig. 5 Plots the numerical solution over 50 simulations on the first run. The experimental measurements are shown as white dots.

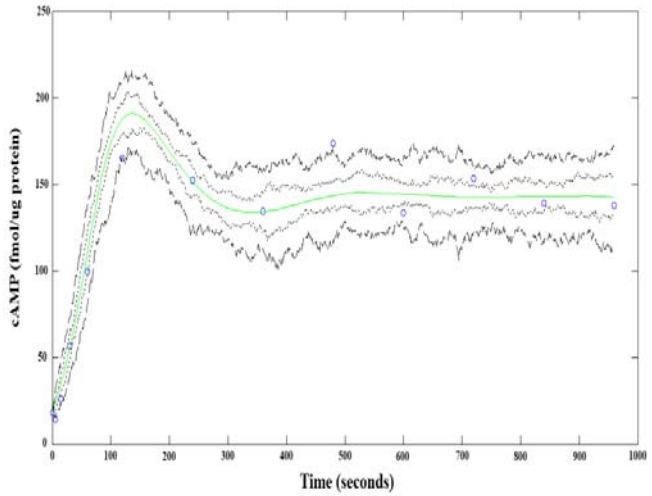

Fig. 6 Plots the empirical mean (green solid line), 95% confidence interval (dashed lines), Q_1 and Q_3 quartiles of the numerical solution (dotted lines) over 50 simulations on the first run. The experimental measurements are shown as empty circles, while the empirical mean is shown here as a solid curve.

We then carried out a third run over 70 simulations and found that the errors associated to all parameter estimates are consistently smaller, as seen in Table III, although the estimates for a_4 and a_6 are still in question.

Thus, we observe that the parameter estimates seem to be more reliable when more simulations are carried out in a run, since the errors are now consistently smaller for all parameters.

The plots of empirical mean, confidence interval and Q_1 and Q_3 quartiles of the identified model, using the parameter estimates in Table III, are shown in Figure 8.

TABLE II

ESTIMATED MODEL PARAMETERS FROM SECOND RUN

parameter	estimated value
a_1	0.86294 ± 0.05192
a_2	0.38193 ± 0.03162
a_3	2.16829 ± 0.71925
a_4	0.03810 ± 0.08376
a_5	0.51923 ± 0.14921
a_6	0.020728 ± 0.14824
b_1	0.30284 ± 0.04289
b_2	0.32078 ± 0.01092
σ	0.03028 ± 0.01093

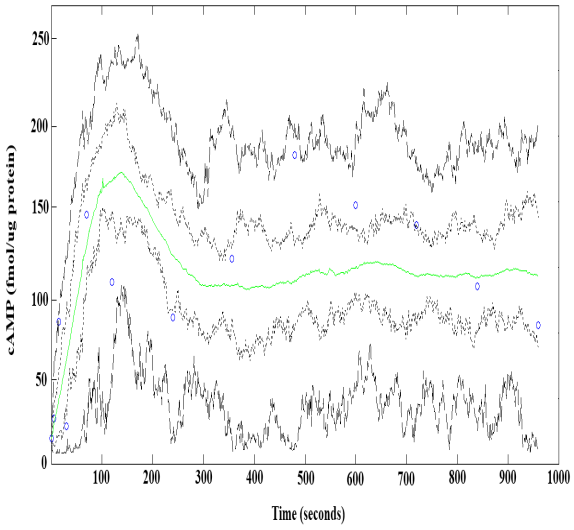

Fig. 7 Plots the empirical mean (green solid line), 95% confidence interval (dashed lines), Q_1 and Q_3 quartiles of the numerical solution (dotted lines) over 50 simulations in the second run. The experimental measurements are shown as empty circles, while the empirical mean is shown here as a solid curve.

TABLE III

ESTIMATED MODEL PARAMETERS ON THE THIRD RUN

parameter	estimated value
a_1	1.15643 ± 0.04536
a_2	0.44894 ± 0.02456
a_3	3.61315 ± 0.08314
a_4	0.04645 ± 0.04215
a_5	0.41766 ± 0.41960
a_6	0.01532 ± 0.10948
b_1	0.21536 ± 0.02393
b_2	0.24483 ± 0.00826
σ	0.01455 ± 0.00354

Considering Tables 1, 2 with Table 3, the errors of the estimated parameter values decrease with more simulations in a run. Thus, the more thorough simulations yield smaller error.

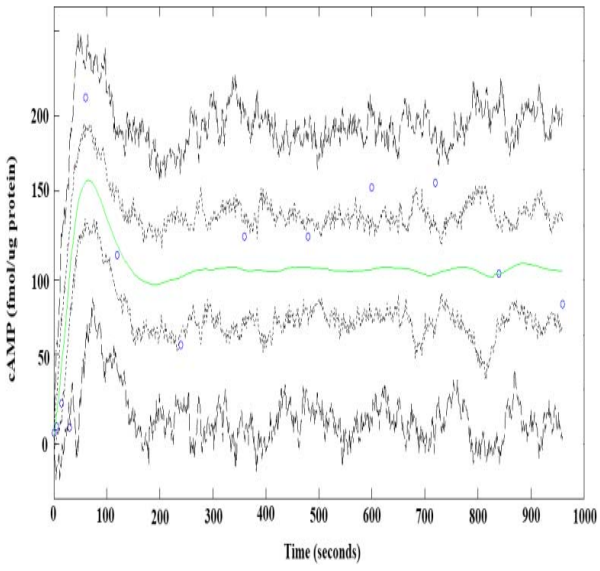

Fig. 8 Plots the empirical mean (green solid line), 95% confidence interval (dashed lines), Q_1 and Q_3 quartiles of the numerical solution (dotted lines) over 70 simulations in the third run. The experimental measurements are shown as empty circles, while the empirical mean is shown here as a solid curve.

Finally, we present the values of the system parameter estimated over 100 simulations in Table IV. The errors are consistently small for all parameters except for possibly a_3.

TABLE IV

ESTIMATED MODEL PARAMETERS
OVER 100 SIMULATIONS

parameter	estimated value
a_1	1.16796 ± 0.16256
a_2	0.61427 ± 0.17978
a_3	1.67558 ± 1.27681
a_4	0.12473 ± 0.06261
a_5	0.20681 ± 0.00296
a_6	0.14282 ± 0.10272
b_1	0.30172 ± 0.00268
b_2	0.35862 ± 0.00284
σ	0.01081 ± 0.00021

By comparison, in [8] Rattanakul et al. utilized a deterministic model to simulate the signaling system and the parameter values were estimated by a genetic algorithm. It may be observed that the parameter estimates obtained from different runs are greatly different from one run to another, and the simulated curves do not approximate the data points that closely, even though the parameter estimates already yielded minimum least squares. This would lead us to conclude that confidence on the reliability of the estimates could not be very high. It would also be difficult to justify our choice of one set of estimates from another.

With the results in this paper, however, we see that the three sets of estimates (in Tables I - III) are relatively close to each other, more or less within the error bars of each corresponding parameter. The parameter values obtained in this manner should thus be more reliable and the identified SDE model can then more properly represent the behavior of the probabilistic dynamics of such a complex system.

To ascertain whether the model with the parameter values obtained in this manner actually approximate the dynamic behavior of the G protein coupled receptors S and that of the inhibiting hormone I closely enough, we need to obtain experimental data on the densities of both quantities which involves complicated controlled experiments which are not currently within our capability.

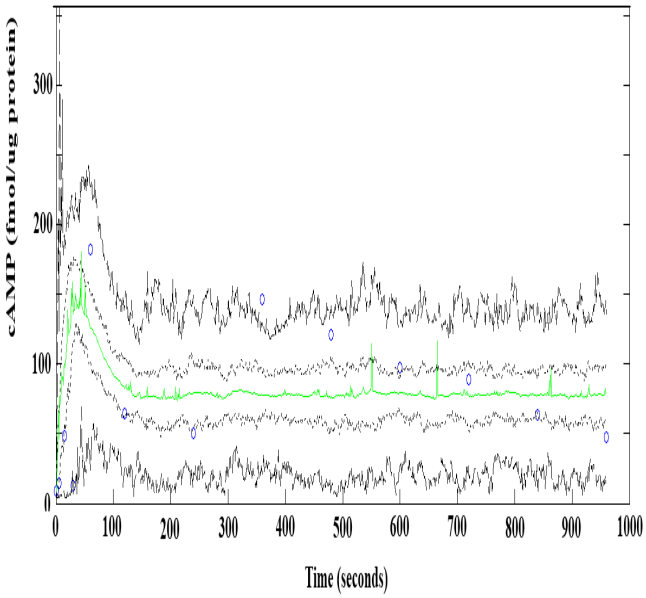

Figure 9 shows the plots the empirical mean, 95% confidence interval, and the Q_1 and Q_3 quartiles of the numerical solution over 100 simulations using the parametric values found in Table IV.

VI. Conclusion

The aim of this paper was to estimate the parameters of the model for the experiment data in signal transduction involving G protein coupled receptors.

We developed a mathematical model by modifying the deterministic model proposed in [8] into stochastic model. Then, we estimated the parameter values by using the Euler - Maruyama Approximation and maximum likelihood estimators. Nine of the unknown parameter values could be estimated moderately well, given the limited data set of only 13 samples. The errors of the estimation parameters will decrease when we more simulation run.

The parameters which we estimated can help the physicians in monitoring abnormality in the cell signaling process which leads to many serious diseases.

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