AN APPROPRIATE INFLOW MODEL FOR SIMULTANEOUS DISSOLUTION AND DEGRADATION

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Abstract. Based on the observed data for Clarithromycin released, three commonly used inflow models: the power, the exponential, and the logarithmic models are considered. Among them, the power model is used most in practice for simplicity. Using the numerical parameter estimation techniques, the parameters appeared in the model equations are estimated. Through the numerical estimation results using the several experimental data sets, the exponential model turns out to be best among the three models. More specifically, the sum of squares of absolute errors and the sum of squares of relative errors for the exponential model are reduced by 80-95 % for the experimental data sets and 60-90 % for the noise added data sets compared with those for the power and logarithmic models. A typical experimental data set is used in this paper to show the estimation method and its numerical results. The proposed numerical method and its algorithm are designed for estimating the parameters appeared in the model differential equations for which the exact form of the solution is unknown in general. The methodology developed can be applied to more general cases such as the nonlinear ordinary differential equations or the partial differential equations.

1. Introduction

Recently, considerable attentions have been focused on the dissolution test of oral dosage forms. It plays an important role both in the development of a new drug product and the quality control of a marketed product[7,10,16,20]. The solubility, the dissolution rate, and the intestinal

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permeability have been considered as the major biopharmaceutic factors that determine the extent and the rate of absorption[15]. The dissolution test becomes more important when a drug is classified as Class II or Class IV in BCS(Biopharmaceutics Classification System)[8,15], since the extent of absorption can be limited by the dissolution rate of the drug. In addition, the dissolution rate of a drug can be correlated with the in vivo results when an appropriate test method is used for the dissolution study. Therefore, it is important to measure the dissolution rate of a drug product accurately using appropriate method for the product. However, when a drug is degraded during dissolution study, the extent of dissolution can be erroneously estimated[10]. Depending on analytical method used, it can be underestimated or overestimated. It has been reported in the literature that some of the drugs could be degraded during the dissolution study[9,11,12,14,16,21]. It is essential to know the amount of drug released and the amount of drug degraded during the dissolution study in the development of suitable formulation for the degrading drug and subsequent quality control of the developed product. If all the degradation products can be quantitatively analyzed, it will be easy to measure both the amount of drug released and the amount degraded. However, it is very difficult to measure the amount of degradation product accurately. Several mathematical approaches have been made to describe simultaneous dissolution and degradation[7,21].

In this study, we develop a mathematical model to estimate the amount of drug released based on the amount of drug left after degradation in the dissolution medium. From the observed data of the model drug, Clarithromycin, an appropriate inflow model is found. Three typical inflow models: the power, the exponential, and the logarithmic models are considered. Among the models, the power model is used most in practice for simplicity. Since the inflow models are given as parts of the corresponding governing differential equations describing the degradation, and the exact forms of the solutions for the equations are unknown in general, the parameters appeared in each model are estimated based on the observed data and the numerical estimation techniques. For the parameter estimation techniques, see [1,3-6,17] and the references therein. For the error analysis, the sum of squares of absolute errors(SSA) and the sum of squares of relative errors(SSR) are considered. From the numerical estimation results, the exponential inflow model turns out to be best among the three proposed models. More specifically, the SSA and the SSR for the exponential inflow model are

reduced by approximately 80-95%, compared with those for the power and the logarithmic models. Also, by allowing the maximum of $\pm 2\%$ random noise on the observation data, the reduction rates of the SSA and the SSR for the exponential model compared to other two models are ranged from 60% to 90%.

In Section 2, the materials and the methods for obtaining the experimental data are explained. The mathematical models and the numerical parameter estimation schemes are described in Section 3. The numerical estimation results using a typical experimental data set are given in Section 4.

2. Materials and methods

2.1. Materials

Clarithromycin was a gift from Chong Kun Dang Pharmaceutical Company (Seoul, Korea). All other chemicals were of reagent grade or above and were used without further purification.

2.2. Release of Clarithromycin from the tablet

Drug release test was carried out using a dissolution tester (DST 810, Labfine, Inc., Korea). Clarithromycin tablets were placed in 900 ml of the dissolution medium at 37°C using USP dissolution apparatus II (paddle method) with a paddle rotating at 50 rpm. The pH of dissolution mediums tested was 1.2. An aliquot of release medium was withdrawn at predetermined time intervals and equivalent amount of fresh medium was added. Withdrawn samples were passed through a $0.45\ \mu\text{m}$ nylon filter and immediately neutralized with 0.1N NaOH solution and analyzed using HPLC (Shimadzu Scientific Instruments, MD, USA) to determine the amount of Clarithromycin released from the tablet.

2.3. Stability of Clarithromycin in pH 1.2 buffer

Stability test was carried out using a dissolution tester (DST 810, Labfine, Inc., Korea). Clarithromycin ($50\ \mu\text{g}/\text{ml}$) was dissolved in pH 1.2 buffer preheated to 37°C . An aliquot of the buffer was withdrawn at predetermined time points. The withdrawn samples were immediately

neutralized with 0.1N NaOH to prevent further degradation. The concentration of Clarithromycin was measured by HPLC system(Shimadzu Scientific Instruments, MD) at the wavelength of 210 nm.

3. Mathematical models and parameter estimation

3.1. Mathematical models

To describe the amount of intact drug left in the dissolution medium, the following differential equation are considered.

$$(1) \quad \frac{d}{dt} Q_{me}(t) = \frac{d}{dt} Q_{in}(t) - k Q_{me}(t), \quad t > 0,$$

$$(2) \quad Q_{me}(0) = 0,$$

where $Q_{me}(t)$ is the amount of the intact drug remaining in the medium(%) measured at time t , $Q_{in}(t)$ is the inflow quantity(the total amount of the drug released, %) at time t , and k is the first order degradation rate constant.

To find an appropriate inflow model, we consider the following three models.

Model 1. Power model: $Q_{in}(t) = a t^n$, where a and n are unknown.

Model 2. Exponential model: $Q_{in}(t) = a(1 - e^{-bt}) + c(1 - e^{-dt})$, where a , b , c , and d are unknown.

Model 3. Logarithmic model: $Q_{in}(t) = y_0 + a \ln(t + b)$, where a and b are unknown, and $y_0 = -a \ln b$ due to $Q_{in}(0) = 0$.

Then, by plugging $Q_{in}(t)$ into equation (1), we have the following governing equations for each model.

$$(3) \quad \frac{d Q_{me}(t)}{dt} = a n t^{n-1} - k Q_{me}(t), \quad Q_{me}(0) = 0$$

for the power model,

$$(4) \quad \frac{d Q_{me}(t)}{dt} = a b e^{-bt} + c d e^{-dt} - k Q_{me}(t), \quad Q_{me}(0) = 0$$

for the exponential model, and

$$(5) \quad \frac{d Q_{me}(t)}{dt} = \frac{a}{t + b} - k Q_{me}(t), \quad Q_{me}(0) = 0$$

for the logarithmic model.

Based on the measurement data of Clarithromycin released, we need to determine which model is best among the above three models. For this purpose, we assume that the governing equations (3)-(5) represent the amount(%) of Clarithromycin remained in the medium. By finding the “optimal” parameters appeared in each model fitting the observed data “best”, we can estimate the amounts $Q_{me}(t)$ of the Clarithromycin remained at the times when the actual measurements are performed. Therefore, by comparing the estimated amounts in each model to the actual measurement ones, we can determine which is the most appropriate model among the proposed models. In these comparison, we also need to take account of measurement random noise errors. Therefore, the essential factor is to find the optimal parameters for each model under a certain accuracy tolerance level. In the following, we consider the general procedure of the parameter estimation for the problems described by the differential equations (3)-(5).

3.2. Parameter estimation

We begin with the actual measurement data set. Let

$$(6) \quad w_i, \quad i = 1, 2, \dots, m,$$

be the observed Clarithromycin remained data(%) measured at time t_i . In each model (3), (4), or (5), the numerically or analytically estimated amounts $Q_{me}(t_i)$, $i = 1, 2, \dots, m$, represent the measured data w_i . Let

$$(7) \quad q = [a, n]^T \quad (q = [a, b, c, d]^T \text{ for (4) and } q = [a, b]^T \text{ for (5)})$$

be the parameters vector appeared in (3) ((4) or (5), respectively), where T stands for the transpose, i.e., q is a column vector. Then we consider the following parameter estimation problem:

Problem 1: Given the set of Clarithromycin measurements w_i in (6), find the optimal parameter vector q^* that minimizes the cost functional

$$(8) \quad J(q) = \sum_{i=1}^m \{Q_{me}(t_i; q) - w_i\}^2,$$

where $Q_{me}(t_i; q)$ is the estimated solution at time t_i for equation (3) ((4) or (5)) with the parameter vector q defined by (7).

The general procedure for solving Problem 1 is following.

Step 1. Choose an initial guess vector $q := q_0$.

- Step 2. From the current q , find a new q_{new} such that $0 \leq J(q_{new}) < J(q)$, and set $q := q_{new}$. Here, J is defined by (8).
 Step 3. Until $J(q)$ reaches the minimum, continue Step 2.

Step 2 is the key step in the optimization process. First of all, for a given parameter vector q , we need to compute $J(q)$. As we see in (8), the computation of $J(q)$ requires the estimated values $Q_{me}(t_i; q)$ for times t_i , $i = 1, 2, \dots, m$. However, $Q_{me}(t; q)$ is the solution of the differential equation (3)((4) or (5)), and the exact form for the solution is unknown in general. Therefore, we need to employ an appropriate numerical method for solving the differential equations. Note that, from the theory of ordinary differential equations, equation (4) has the exact solution given by

$$(9) \quad Q_{me}(t) = \frac{a b}{k - b} \left(e^{-bt} - e^{-kt} \right) + \frac{c d}{k - d} \left(e^{-dt} - e^{-kt} \right).$$

The purpose of this paper is to provide a general parameter estimation method for solving the problems for which the exact solution forms are unknown as in the cases (3) and (5). Thus, we will consider the efficient and accurate numerical integration methods to which all the cases (3)-(5) can be applied.

Another important issue in Step 2 is to find a new parameter vector q_{new} from the current one q_{cur} satisfying $J(q_{new}) < J(q_{cur})$. To find a descent direction for $J(q)$, we need the information on $\nabla_q J(q)$, the gradient of J with respect to the parameter q , or equivalently, $\nabla_q Q(t; q)$, the gradient of $Q(t; q)$ with respect to q . Since $Q(t; q)$ is not available in an exact form as mentioned before, we need a numerical scheme for approximating $\nabla_q Q(t; q)$. In this step, several time integrations will be needed. Also, a robust optimization method is needed due to the highly nonlinear dependency of $Q(t; q)$ on q . Also, note that, at each iteration for updating q , the computations for $\nabla_q Q(t; q)$, and, hence, many time integrations for solving the differential equations (3)((4) or (5)) are required.

The stopping criterion for Step 3 can be given by $|J(q_{new}) - J(q_{cur})| < tol$ for an appropriate accuracy tolerance, equivalently, by $|q_{new} - q_{cur}| < tol$ for many cases. From the brief explanation for Steps 2-3, in essential, many numerical integration methods for the differential equations

(3)((4) or (5)) are required to obtain the optimal parameter q^* minimizing the cost functional $J(q)$. Thus, the parameter estimation method should fulfill the following conditions:

- (i) The time integration solver for the differential equations should be efficient and accurate.
- (ii) The formulation for computing $\nabla_q Q(t; q)$ should be simple, but, should produce accurate approximation.
- (iii) The descent direction search algorithm should be robust.

Considering those aspects mentioned above, we will derive our parameter estimation algorithm.

3.2.1. Time integration. We now consider the numerical integration methods for solving the differential equations (3)-(5). There are many integration methods such as the Runge-Kutta method, the Crank-Nicolson method, multi-step methods, semi-implicit methods, etc.[2,19,22]. Since the equations are linear and relatively simple, the 4-th order Runge-Kutta method is employed in this paper to maintain the stability, convergency, accuracy, and efficiency. The total computational costs are within a few seconds.

The basic idea of the 4-th order Runge-Kutta method for solving the differential equation

$$(10) \quad \frac{d}{dt}Q(t; q) = f(t, Q(t; q))$$

can be approximated by

$$(11) \quad Q(t + \Delta t; q) = Q(t; q) + \frac{\Delta t}{6} \{K_1 + 2K_2 + 2K_3 + K_4\},$$

where $Q(t; q) = Q_{me}(t; q)$, $f(t, Q(t; q))$ represents the right hand side of equations (3), (4), or (5), Δt is the time step for integration, and

$$(12) \quad K_1 = f(t, Q(t; q)),$$

$$(13) \quad K_2 = f\left(t + \frac{\Delta t}{2}, Q(t; q) + \frac{\Delta t}{2}K_1\right),$$

$$(14) \quad K_3 = f\left(t + \frac{\Delta t}{2}, Q(t; q) + \frac{\Delta t}{2}K_2\right),$$

$$(15) \quad K_4 = f(t + \Delta t, Q(t; q) + \Delta t K_3),$$

and the parameter vector q is given by $q = [a, n]^T$, $q = [a, b, c, d]^T$, and $q = [a, b]^T$ for equations (3), (4), and (5), respectively. From equation (11), the estimated Clarithromycin amounts $Q(t_i; q)$, and, hence, $J(q)$

in (8) can be obtained for each given time t_i and the parameter vector q . From now on, $Q_{me}(t)$ will be denoted by $Q(t)$ for notational purpose.

3.2.2. Calculation of $\nabla_q Q(t; q)$. This step is for computing $\nabla_q J(q)$, the gradient of the cost function J in (8), which is needed for finding a new parameter q_{next} from the current one q_{cur} . Since this process involves the time integration for $Q(t; q)$, it would be better to reduce the number of integrations, because the time integrations, i.e., solving the differential equations, are main sources for the computational costs required by the optimization process. Conventionally, Euler type method is used for the calculation of $\nabla_q Q(t; q)$. However, we use the central difference method to obtain the accuracy, efficiency, and stability for our approximation scheme. Let q be a parameter vector given by

$$(16) \quad q = [q_1, q_2, \dots, q_l]^T,$$

where q_i is the parameters to be estimated for each model and l is the number of parameters. That is, $l = 2$ for the power and the logarithmic models and $l = 4$ for the exponential model, and $a = q_1$, $n = q_2$, $a = q_1$, $b = q_2$, $c = q_3$, $d = q_4$, and $a = q_1$, $b = q_2$ in (11) for each model. Then we have the following approximation for the gradient of $Q(t; q)$ with respect to the parameter vector q .

$$(17) \quad \nabla_q Q(t; q) = \left[\frac{\partial Q(t; q)}{\partial q_1}, \frac{\partial Q(t; q)}{\partial q_2}, \dots, \frac{\partial Q(t; q)}{\partial q_l} \right]^T,$$

where, for each $i = 1, 2, \dots, l$, $\frac{\partial Q(t; q)}{\partial q_i}$ is approximated by the central difference:

$$(18) \quad \frac{\partial Q(t; q)}{\partial q_i} = \frac{Q(t; \hat{q}_i^+) - Q(t; \hat{q}_i^-)}{2\Delta q_i},$$

$$(19) \quad Q(t; \hat{q}_i^+) = Q(t; q_1, \dots, q_{i-1}, q_i + \Delta q_i, q_{i+1}, \dots, q_l),$$

$$(20) \quad Q(t; \hat{q}_i^-) = Q(t; q_1, \dots, q_{i-1}, q_i - \Delta q_i, q_{i+1}, \dots, q_l),$$

where Δq_i is a sufficiently small positive number. Note that two time integrations for $Q(t; q)$ are needed for each time t to obtain (18) for each $i = 1, 2, \dots, l$. Since we need the information on $\frac{\partial Q(t_j; q)}{\partial q_i}$ for each time t_j , $j = 1, 2, \dots, m$, by saving the previous computational results $\frac{\partial Q(t_{j-1}; q)}{\partial q_i}$, the actual computational costs are similar to those for the Euler type method. In order words, by the approximation (18), we can obtain the high accuracy with almost minimum computational costs. Also, this approximation is stable by using the balanced information $Q(t; \hat{q}_i^+)$ and $Q(t; \hat{q}_i^-)$. These are the strong points of employing the central difference

method for approximating the gradient of $Q(t; q)$ with respect to each component q_i .

3.2.3. Descent direction and algorithm. We now consider the problem for finding a new parameter vector q_{next} from the current one q_{cur} satisfying the condition $0 \leq J(q_{next}) < J(q_{cur})$. Updating the parameter vector q has the following form:

$$(21) \quad q_{next} = q_{cur} + \delta,$$

where δ is an appropriate vector to be chosen so that $J(q_{next}) < J(q_{cur})$. Many optimization methods have been developed based on how to choose δ in (21)[1,3,5,18]. Since our optimization problem has high nonlinear dependence upon q , a modified Levenberg-Marquardt method[18] will be considered.

Consider the following residual vector.

$$(22) \quad R(q) = [R_1(q), R_2(q), \dots, R_m(q)]^T, \quad R_i(q) = Q(t_i; q) - w_i,$$

where $Q(t_i; q)$ are the estimated quantities obtained by solving equation (11) for each model), w_i are the actual measurement data as in (6), and m is the number of measurements. The next step is to find the gradient of the residual vector $R(q)$ with respect to q . Let $\nabla_q R$ be the gradient of R . Then, from equation (22), we have

$$(23) \quad \nabla_q R = [\nabla_q R_1, \nabla_q R_2, \dots, \nabla_q R_m]^T$$

$$(24) \quad = [\nabla_q Q(t_1; q), \nabla_q Q(t_2; q), \dots, \nabla_q Q(t_m; q)]^T,$$

where each $\nabla_q R_i = \nabla_q Q(t_i; q)$ is obtained by the central difference method as in (18). Thus, $\nabla_q R(q)$ becomes $m \times 2$, $m \times 4$, and $m \times 2$ matrices for the power, the exponential, and the logarithmic models, respectively.

The next step is to choose the scalar parameter $\lambda > 0$ satisfying the condition that the matrix $(\nabla_q R)^T (\nabla_q R) + \lambda I$ to be positive definite, where I is the identity matrix. By controlling the parameter λ , we can find a descent direction δ in (21) so that $J(q_{next}) < J(q_{cur})$ is satisfied. More precisely, the direction δ in (21) is obtained by solving the following matrix-vector equation:

$$(25) \quad [(\nabla_q R)^T (\nabla_q R) + \lambda I] \delta = -(\nabla_q R)^T R(q).$$

Note that for a small λ , the system (25) is similar to Newton Method, and for a large λ , it becomes the Steepest Descent Method[22]. In practice, we choose the parameter λ as the following way. Start with an initial guess, say, $\lambda = 0.001$, solve equation (25) for δ , set $q_{temp} = q_{cur} + \delta$, compute $J(q_{temp})$, and compare it with $J(q_{cur})$. If $J(q_{temp})$ is bigger than $J(q_{cur})$, make λ bigger, for example, multiply λ by 10, and continue these process until the condition $J(q_{temp}) < J(q_{cur})$ is satisfied. Once we find the descent direction, update λ by, for example, dividing λ by 10, update q by setting $q_{next} = q_{cur} + \delta$, and continue these steps until $J(q)$ reaches the minimum. Since the minimum value of the cost function $J(q)$ is unknown in advance, the following stopping criterion:

$$(26) \quad |J(q_{cur}) - J(q_{next})| \leq Tol,$$

or, equivalently,

$$(27) \quad |q_{next} - q_{cur}| = \sum_{i=1}^l |q_{next}(i) - q_{cur}(i)| \leq Tol$$

can be used in practice. Here, Tol is the minimum tolerance value for the convergence of the parameter vectors.

We now summarize our discussion above as the following algorithm, the Central Difference Levenberg-Marquardt Method(CDLMM). The stopping criterion (27) is used for the following algorithm.

Algorithm 2.1(CDLMM)

0. Input: The first order degradation rate constant k in (1), the number of measurements m , and the data set $w = [w_1, w_2, \dots, w_m]^T$ measured at times $t_1, \dots, t_m$ in (6).
1. Choose the maximum iteration number $imax$, the tolerance Tol for (26) or (27), the time step Δt for (11), and the sufficiently small numbers Δq_i , $i = 1, 2, \dots, l$ for (18).
2. Choose an initial parameter $q := q_0$ in (16).
3. Do Steps 4-9 until the stopping criterion (26) or (27) is satisfied.
4. Choose an initial scalar parameter $\lambda := \lambda_0$ in (25).
5. For $i = 1, 2, \dots, m$, do Steps 5.1 - 5.3.
 - 5.1. Find $Q(t_i; q)$ by using the numerical integration formula (11).
 - 5.2. Set the residual $R_i = Q(t_i; q) - w_i$.
 - 5.3. Find $\frac{\partial Q(t_i; q)}{\partial q_i}$ by (18)-(20).
6. Compute the cost $J_{cur} := \sum_{i=1}^m (R_i)^2$.
7. Set $J_{next} = J_{cur}$ and the iteration counting number $ic = 0$.

8. While $J_{next} > J_{cur}$ and $ic < imax$, do Steps 8.1-8.7.

8.1. Form $\nabla_q R$ by equation (23)-(24).

8.2. Find the direction vector δ from equation (25).

8.3. Let $q = q + \delta$.

8.4. Do Step 5.

8.5. Compute $J_{next} = \sum_{i=1}^m (R_i)^2$.

8.6. if $J_{next} > J_{cur}$, let $\lambda = \lambda * 10$,
else let $\lambda = \lambda * 0.1$.

8.7. Set $ic = ic + 1$.

9. Set $q_{next} = q + \delta$.

3.2.4. Error analysis. To find the most appropriate inflow model among the three given models, the sum of squares of absolutely errors(SSA) and the sum of squares of relative errors(SSR) can be used for each model. The SSA and the SSR are defined by the following.

$$(28) \quad SSA = \sum_{i=2}^m (Q_{me}(t_i; q) - w_i)^2 \quad \text{and} \quad SSR = \sum_{i=2}^m \left(\frac{Q_{me}(t_i; q) - w_i}{w_i} \right)^2,$$

where m is the number of measurements. Note that the summations in the SSA and the SSR start from $i = 2$ due to the fact that $Q_{me}(0; q) = w_0 = 0$.

4. Numerical results

The decomposition rate constant k in equation (1) and the measured Clarithromycin remained data(%) for k are shown in Figure 1. In Figure 1, the the measured data are shown as circles and the fitted function $100 \exp(-kt)$ with the estimated decomposition rate $k = 0.4681$ is shown as a solid line.

To determine the best model among the three proposed inflow models, we used the measured Clarithromycin data(%) released with pH 1.2. Also, we performed several numerical simulations using the several noise added data with the maximum relative random noise level of $\pm 2\%$. The measured data and one of typical noise added data are shown in Table 1.

For the numerical estimation of the parameters appeared in the three models, the decomposition rate $k = 0.4681$, the small numbers $\epsilon = 0.001$ and $\delta = 0.001$ for approximating the gradients of the cost function J

FIGURE 1. Measured data(o) and $100 \exp(-0.4681 t)$.

TABLE 1. Clarithromycin measured data

time(h)	measured data(%)	data with max $\pm 2\%$ noise
0.0000	0.0000	0.0000
1.0000	27.8524	28.1482
2.0000	27.2115	27.5328
3.0000	23.6408	23.3447
4.0000	20.4887	20.4803
5.0000	16.5910	16.5549
6.0000	13.5043	13.5833

in (8), the maximum number of iterations $imax = 100$, the time step $\Delta t = 0.001$, and the convergence tolerance $Tol = 10^{-6}$ were chosen. The stopping criterion (27) was chosen to see the convergence of the parameters to be estimated. For all the models, the numbers of iterations for the convergence of the parameters q were less than 10 for a wide range of initial guesses, and their computational costs were only a few seconds on a PC with the Pentium 4 processor. The estimated parameters, their SSA and SSR for the proposed three models with the measured data and for the noise added data in Table 1 are shown in Tables 2 and 3.

From Table 2, one can observe that, for the measured data, the SSA and the SSR for the exponential inflow model are reduced approximately

TABLE 2. Estimated parameters, SSA, SSR for measured data.

Model	Estimated parameter	SSA	SSR
Power	$a = 42.4389, n = 0.3488$	1.8393	6.5762×10^{-3}
Exponential	$a = 23.6733, b = 3.0677$ $c = 63.1925, d = 0.2660$	0.1505	3.3049×10^{-4}
Logarithmic	$a = 23.1652, b = 0.2604$	0.9527	1.7602×10^{-3}

TABLE 3. Estimated parameters, SSA, SSR for data with maximum $\pm 2\%$ noise.

Model	Estimated parameter	SSA	SSR
Power	$a = 43.0537, n = 0.3432$	1.6155	5.0905×10^{-3}
Exponential	$a = 26.6801, b = 2.4530$ $c = 62.9836, d = 0.2329$	0.4070	8.6333×10^{-4}
Logarithmic	$a = 22.8511, b = 0.2470$	1.2257	2.5293×10^{-3}

by 92% and 95% compared with those for the power model, and by 84% and 81% to the logarithmic model, respectively. For the noise added data, the corresponding reduction rates of the SSA and the SSR for the exponential model were 75% and 83% to the power model, and 67% and 66% for the logarithmic model, respectively. The numerical simulation results for several other random noised data sets showed that the reduction rates of the exponential model to the power and the logarithmic models were approximately 70-90%, 60-80% for the SSA and 80-90%, 60-80% for the SSR, respectively. Therefore, based on the numerical simulation results, we can conclude that the exponential inflow model is superior to the power and the logarithmic models. The estimation results for the exponential inflow model are shown for the original measured data in Figure 2 and for the noise added data in Figure 3.

5. Concluding remarks

Based on the Clarithromycin measured data released at pH 1.2, we have considered three inflow models: the power, the exponential, and

FIGURE 2. Exponential model: inflow $Q_{in}(t)(-)$, measured data(o), estimated $Q_{me}(t)(- -)$.

FIGURE 3. Exponential model(with noise): inflow $Q_{in}(t)(-)$, noised data(o), estimated $Q_{me}(t)(- -)$.

the logarithmic models. The parameters appeared in each model were estimated by the parameter estimation techniques. From the numerical simulations and the error analysis for the measured data and the random noise added data, we can conclude that the exponential model is the best among the three proposed inflow models. The numerical parameter estimation techniques described in this paper can be applied, particularly, to the problems for which the closed form of analytic solution for the governing equations are unknown. Those problems often involve

the nonlinear ordinary differential equations and the partial differential equations.

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