The CRLB for Bilinear Systems and Its Biomedical Applications

Zhiping Lin, Qiyue Zou
Centre for Signal Processing
School of Electrical and Electronic Engineering
Nanyang Technological University, Singapore 639798
Email: ezplin@ntu.edu.sg

Raimund J. Ober
Center for Systems, Communications and Signal Processing
Eric Jonsson School of EECS
University of Texas at Dallas
Richardson, TX 75083-0688, USA

***Abstract*— The Cramer Rao lower bound (CRLB) provides a lower bound on the covariance matrix of any unbiased estimator of unknown parameters. It is shown in this paper that the CRLB for a data set generated by a bilinear system with additive Gaussian measurement noise can be expressed explicitly in terms of the outputs of its derivative system which is also bilinear. For bilinear systems with piecewise constant inputs the CRLB for uniformly sampled data can be efficiently computed through solving certain Lyapunov equations. The theoretical results are illustrated through an example arising from surface plasmon resonance experiments for the determination of the kinetic parameters of protein-protein interactions.**

I. Introduction

A fundamental problem in biomedical applications is to estimate unknown system parameters from output observations [1]. Although there are many methods for parameter estimations for linear systems, it is well known that linear models are not appropriate for some biomedical applications and hence bilinear and/or nonlinear system models have to be used [1], [2]. For parameter estimation for bilinear systems which will be discussed in this paper, an important question is the accuracy of the estimation that can be achieved based on the observed noisy outputs. The Cramer Rao lower bound (CRLB) gives a lower bound on the covariance matrix of any unbiased estimator of unknown parameters [3]. It is commonly used to evaluate the performance of an estimation algorithm and can provide guidance to improve the experimental design.

The CRLB or Fisher information matrix for one-dimensional (1D) dynamic non-stationary systems with deterministic input and Gaussian measurement noise has been investigated in [4]. The calculation of the Fisher information matrix for the 1D data is performed in terms of the derivative system with respect to the system parameters and by using the solution to a Lyapunov equation. The above approach has been extended to multidimensional (nD) data sets generated by nD linear separable-denominator systems and applied to the analysis of nD nuclear magnetic resonance spectroscopy data sets [5].

Here we generalize the results in [4] to bilinear systems. It is shown that the Fisher information matrix for the output data samples of a multiple-input-multiple-output (MIMO) bilinear system can be expressed in terms of the outputs of its derivative system which is also an MIMO bilinear system. The notion of derivative system is very useful in that it gives an explicit expression for the Fisher information matrix and the CRLB. Furthermore, for uniformly sampled data sets, the CRLB can be efficiently computed using algorithms based on solutions to certain Lyapunov equations. The results are then applied to estimation of kinetic constants of protein-protein interactions arising from surface plasmon resonance experiments [2], [6].

II. Cramer Rao Lower Bound

Consider the state-space model of a general MIMO bilinear system given by (see [7])

$$\dot{x}_\theta(t) = Ax_\theta(t) + \sum_{q=1}^{m} F_q u_q(t) x_\theta(t) + Bu(t),\ x_\theta(t^{[0]}) = x_0, \tag{1}$$

$$y_\theta(t) = Cx_\theta(t), \quad t \geq t^{[0]}, \tag{2}$$

where $x_\theta(t) \in \mathbb{R}^{n\times 1}$ is the state vector, $u(t) \in \mathbb{R}^{m\times 1}$ is the input vector with components $u_1(t)$, ..., $u_m(t)$, $y_\theta(t) \in \mathbb{R}^{p\times 1}$ is the system output vector, $A \in \mathbb{R}^{n\times n}$, $B \in \mathbb{R}^{n\times m}$, $C \in \mathbb{R}^{p\times n}$, $F_q \in \mathbb{R}^{n\times n}$, $q = 1, \ldots, m$, are the system matrices depending on the unknown parameter vector $\theta := \begin{bmatrix} \theta_1 & \ldots & \theta_K \end{bmatrix}^T$, and x_0 is the initial state vector, which can also depend on the parameter vector θ. The i^{th} element of $y_\theta(t)$ is represented by $y_{\theta,i}(t)$, and the i^{th} row of C is denoted by C_i, $i = 1, \ldots, p$.

In this paper, we consider only piecewise constant inputs $\mathbb{U}$ represented by

$$u(t) = \sum_{l=0}^{L-1} u^{[l]} \beta_l(t), \quad t^{[0]} \leq t < t^{[L]}, \tag{3}$$

where $u^{[l]} := \begin{bmatrix} u_1^{[l]} & \ldots & u_m^{[l]} \end{bmatrix}^T$ are constant vectors, and $\beta_l(t)$ $(l = 0, \ldots, L-1)$ are the indicator functions defined by

$$\beta_l(t) = \begin{cases} 1, & \text{for } t \in \left[t^{[l]},\ t^{[l+1]}\right), \\ 0, & \text{for } t \notin \left[t^{[l]},\ t^{[l+1]}\right). \end{cases} \tag{4}$$

Here, $t^{[0]}$, ..., $t^{[L]}$ denote the starting and ending points of the time intervals with $t^{[0]} < \ldots < t^{[L]}$, where $t^{[L]}$ can be either finite or infinite. Note that $u^{[l]}$ could be a zero vector, and that for a piecewise constant input $u \in \mathbb{U}$ as defined in (3)

we are only interested in the output $y_\theta(t)$ for $t^{[0]} \le t < t^{[L]}$. We denote $L_1 := L - 1$ throughout. For more general inputs and proofs of the results presented here, see [8].

Lemma 2.1: Consider the bilinear system $\Phi = \{A,\ B,\ C,\ F_1,\ \ldots,\ F_m\}$. Let $F^{[l]} := \sum_{q=1}^{m} F_q u_q^{[l]}$ and assume that $A + F^{[l]}$ is invertible, $l = 0, \ldots, L_1$. Then the output of the system is given by

$$y_\theta(t) = \sum_{l=0}^{L_1} \left[CQ_l(t) \left(W^{[l]} + x_\theta(t^{[l]}) \right) - CW^{[l]} \right] \beta_l(t), \quad (5)$$

where $Q_l(t) := e^{(A+F^{[l]})(t-t^{[l]})}$ and $W^{[l]} := (A + F^{[l]})^{-1} B u^{[l]}$, $l = 0, \ldots, L_1$, and $x_\theta(t^{[l]})$ is given by

$$x_\theta(t^{[l]}) = \begin{cases} x_0, & l = 0, \\ Q_{l-1}(t^{[l]}) \left(W^{[l-1]} + x_\theta(t^{[l-1]}) \right) - W^{[l-1]}, & l = 1, \ldots, L_1. \end{cases}$$

The following assumptions are made throughout the paper. Assume that we have acquired noise corrupted samples $s_{\theta,i}(j)$, $i = 1, \ldots, p,\ j = 0, \ldots, J-1$, of the measured output of the bilinear system, i.e.,

$$s_{\theta,i}(j) = y_{\theta,i}(t_j) + w_i(j), \quad (6)$$

where $y_{\theta,i}(t_j)$ is the i^{th} noise free output element at the sampling point t_j and $w_i(j)$ is the measurement noise component, $i = 1, \ldots, p,\ j = 0, \ldots, J-1,\ t^{[0]} \le t_0 < t_1 < \ldots < t_{J-1}$. The measurement noise components are assumed to have independent Gaussian distributions with zero mean and variance $\sigma_{i,j}^2$, $i = 1, \ldots, p,\ j = 0, \ldots, J-1$. Hence the probability density function $p(S;\theta)$ for the acquired data set $S := \{s_{\theta,i}(j),\ i = 1, \ldots, p,\ j = 0, \ldots, J-1\}$ is given by

$$p(S;\theta) = \prod_{i=1}^{p} \prod_{j=0}^{J-1} \frac{1}{\sqrt{2\pi\sigma_{i,j}^2}} \exp\left(-\frac{1}{2\sigma_{i,j}^2} \left[s_{\theta,i}(j) - y_{\theta,i}(t_j) \right]^2 \right).$$

Assume $p(S;\theta)$ satisfies the standard regularity conditions (see e.g. [3]). The Fisher information matrix $I(\theta)$ is then defined as

$$[I(\theta)]_{sr} = E\left\{ \left(\frac{\partial \ln p(S;\theta)}{\partial \theta_s} \right) \left(\frac{\partial \ln p(S;\theta)}{\partial \theta_r} \right) \right\}, 1 \le s, r \le K,$$

by the CRLB any unbiased estimator $\hat{\theta}$ of θ has a variance such that

$$\mathrm{var}(\hat{\theta}) \ge I^{-1}(\theta),$$

where $\mathrm{var}(\hat{\theta}) \ge I^{-1}(\theta)$ is interpreted as meaning that the matrix $(\mathrm{var}(\hat{\theta}) - I^{-1}(\theta))$ is positive semidefinite.

In the following theorem we first show that the derivative system (with respect to the given parameter vector θ) of a general MIMO bilinear system is also an MIMO bilinear system. The Fisher information matrix for the sampled output data of the bilinear system for Gaussian measurement noise is then expressed using the output samples of its derivative system.

Theorem 2.1: Consider the bilinear system represented by $\Phi = \{A,\ B,\ C,\ F_1,\ \ldots,\ F_m\}$. Assume that the partial derivatives of A, B, C, F_1, ..., F_m and x_0 with respect to the elements of θ exist for all $\theta \in \Theta$, and that the input $u(t)$ is independent of the parameter vector θ. Let

$$\mathcal{Y}_\theta(t) := \begin{bmatrix} \mathcal{Y}_{\theta,1}(t) \\ \vdots \\ \mathcal{Y}_{\theta,p}(t) \end{bmatrix}, \quad with$$

$$\mathcal{Y}_{\theta,i}(t) := \begin{bmatrix} \frac{\partial y_{\theta,i}(t)}{\partial \theta_1} \\ \vdots \\ \frac{\partial y_{\theta,i}(t)}{\partial \theta_K} \end{bmatrix} \ (i = 1, \ldots, p)\ , \quad t \ge t^{[0]}.$$

Then, 1.) $\mathcal{Y}_\theta(t)$, $t \ge t^{[0]}$, is the output of the derivative system $\Phi' := \{\mathcal{A},\ \mathcal{B},\ \mathcal{C},\ \mathcal{F}_1,\ \ldots,\ \mathcal{F}_m\}$, which is an MIMO time-invariant bilinear system with state vector $\mathcal{X}_\theta(t)$, $t \ge t^{[0]}$, and has the same input u as Φ. The state vector $\mathcal{X}_\theta$, initial state $\mathcal{X}_0$, and system matrices $\mathcal{A}$, $\mathcal{B}$, $\mathcal{C}$, $\mathcal{F}_1$, ..., $\mathcal{F}_m$ are given as follows.

$$\mathcal{X}_\theta(t) := \begin{bmatrix} \partial_1 x_\theta(t) \\ \vdots \\ \partial_K x_\theta(t) \end{bmatrix}, \mathcal{X}_0 := \begin{bmatrix} \partial_1 x_\theta(t^{[0]}) \\ \vdots \\ \partial_K x_\theta(t^{[0]}) \end{bmatrix},$$

$$\mathcal{A} := \mathrm{diag}\,\{\partial_1 A, \ldots, \partial_K A\}, \mathcal{B} := \begin{bmatrix} \partial_1 B \\ \vdots \\ \partial_K B \end{bmatrix}, \mathcal{C} := \begin{bmatrix} \mathcal{C}_1 \\ \vdots \\ \mathcal{C}_p \end{bmatrix}$$

$$\mathcal{C}_i := \mathrm{diag}\,\{\partial_1 C_i, \ldots, \partial_K C_i\},\ i = 1, \ldots, p,$$

$$\mathcal{F}_q := \mathrm{diag}\,\{\partial_1 F_q, \ldots, \partial_K F_q\},\ q = 1, \ldots, m,$$

where for $s = 1, \ldots, K$

$$\partial_s x_\theta(t) := \begin{bmatrix} x_\theta(t) \\ \frac{\partial x_\theta(t)}{\partial \theta_s} \end{bmatrix}, \partial_s x_\theta(t^{[0]}) := \begin{bmatrix} x_0 \\ \frac{\partial x_0}{\partial \theta_s} \end{bmatrix},$$

$$\partial_s A := \begin{bmatrix} A & 0 \\ \frac{\partial A}{\partial \theta_s} & A \end{bmatrix}, \partial_s B := \begin{bmatrix} B \\ \frac{\partial B}{\partial \theta_s} \end{bmatrix}, \partial_s C_i := \begin{bmatrix} \frac{\partial C_i}{\partial \theta_s} & C_i \end{bmatrix},$$

$$\partial_s F_q := \begin{bmatrix} F_q & 0 \\ \frac{\partial F_q}{\partial \theta_s} & F_q \end{bmatrix},\ q = 1, \ldots, m;$$

2.) The Fisher information matrix is given by

$$I(\theta) = \sum_{i=1}^{p} \sum_{j=0}^{J-1} \frac{1}{\sigma_{i,j}^2} P_i \mathcal{Y}_\theta(t_j) \mathcal{Y}_\theta^T(t_j) P_i^T. \quad (7)$$

Here $P_i \in \mathbb{R}^{K \times pK}$, $i = 1, \ldots, p$, is defined as

$$P_i = [\ \underbrace{\mathbf{0}\ \ \ldots\ \ \mathbf{0}}_{(i-1)\ \mathbf{0}s}\ \ I_K\ \ \underbrace{\mathbf{0}\ \ \ldots\ \ \mathbf{0}}_{(p-i)\ \mathbf{0}s}\ ]\ , \quad (8)$$

where $\mathbf{0}$ denotes the $K \times K$ zero matrix and I_K the $K \times K$ identity matrix.

For the data set generated by a bilinear system with a piecewise constant input $u \in \mathbb{U}$, the following corollary derives an explicit expression of its associated Fisher information matrix.

Corollary 2.1: Assume that the bilinear system model and assumptions are the same as in Theorem 2.1, and that $A + F^{[l]}$ is invertible, where $F^{[l]} := \sum_{q=1}^{m} F_q u_q^{[l]}$, $l = 0, \ldots, L_1$. Let

$\mathcal{F}^{[l]} := \text{diag}\{\partial_1 F^{[l]}, \ \ldots, \ \partial_K F^{[l]}\}$, $l = 0, \ldots, L_1$, where for $s = 1, \ldots, K$

$$\partial_s F^{[l]} := \begin{bmatrix} F^{[l]} & 0 \\ \frac{\partial F^{[l]}}{\partial \theta_s} & F^{[l]} \end{bmatrix} = \sum_{q=1}^{m} \begin{bmatrix} F_q & 0 \\ \frac{\partial F_q}{\partial \theta_s} & F_q \end{bmatrix} u_q^{[l]}.$$

Then, the output of the derivative system Φ' is given by

$$\mathcal{Y}_\theta(t) = \sum_{l=0}^{L_1} \left[\mathcal{C}\mathcal{Q}_l(t) \left(\mathcal{W}^{[l]} + \mathcal{X}_\theta(t^{[l]}) \right) - \mathcal{C}\mathcal{W}^{[l]} \right] \beta_l(t), \quad (9)$$

where $\mathcal{Q}_l(t) := e^{(\mathcal{A}+\mathcal{F}^{[l]})(t-t^{[l]})}$, $\mathcal{W}^{[l]} := \left(\mathcal{A} + \mathcal{F}^{[l]}\right)^{-1} \mathcal{B}u^{[l]}$, $l = 0, \ldots, L_1$, and

$$\mathcal{X}_\theta(t^{[l]}) = \begin{cases} \mathcal{X}_0, & l = 0, \\ \mathcal{Q}_{l-1}(t^{[l]}) \left(\mathcal{W}^{[l-1]} + \mathcal{X}_\theta(t^{[l-1]}) \right) - \mathcal{W}^{[l-1]}, & l = 1, \ldots, L_1. \end{cases}$$

When the output of a bilinear system is sampled uniformly, the associated Fisher information matrix and the CRLB can be computed efficiently through solving certain Lyapunov equations, as shown in the following theorem.

Theorem 2.2: Assume that the data model is the same as in Corollary 2.1, and that the output signal is uniformly sampled with the sampling period T_l in the l^{th} interval of the piecewise constant input, i.e., at $t_{j^{[l]}}^{[l]} = t^{[l]} + t^{[l,0]} + j^{[l]} T_l$, $j^{[l]} = 0, \ldots, J^{[l]} - 1$, $t^{[l]} \leq t_{j^{[l]}}^{[l]} < t^{[l+1]}$, where $t_{j^{[l]}}^{[l]}$ denotes the ${j^{[l]}}^{th}$ sampling instant in the l^{th} interval, $t^{[l,0]}$ is the starting time relative to $t^{[l]}$ for sampling in the l^{th} interval , and $J^{[l]}$ is the total number of samples acquired in the l^{th} interval, $l = 0, \ldots, L_1$, and the independent measurement Gaussian noise variance ${\sigma_{i,j}^{[l]}}^2 = \sigma^2$, $i = 1, \ldots, p$, $j = 0, \ldots, J^{[l]} - 1$, for $l = 0, \ldots, L_1$. Then the Fisher information matrix for the given data set is

$$I(\theta) = \frac{1}{\sigma^2} \cdot \sum_{i=1}^{p} P_i \mathcal{C} \left\{ \sum_{l=0}^{L_1} \left[\left(\mathcal{A}_d^{[l]} \right)^{\frac{t^{[l,0]}}{T_l}} \mathcal{P}_1^{[l]} \left(\left(\mathcal{A}_d^{[l]} \right)^{\frac{t^{[l,0]}}{T_l}} \right)^T - \left(\mathcal{A}_d^{[l]} \right)^{\frac{t^{[l,0]}}{T_l}} \right. \right. \quad (10)$$
$$\left. \left. \cdot \mathcal{P}_2^{[l]} - \left(\mathcal{P}_2^{[l]} \right)^T \left(\left(\mathcal{A}_d^{[l]} \right)^{\frac{t^{[l,0]}}{T_l}} \right)^T + J^{[l]} \mathcal{W}^{[l]} \left(\mathcal{W}^{[l]} \right)^T \right] \right\} \mathcal{C}^T P_i^T,$$

where $\mathcal{P}_1^{[l]}$ and $\mathcal{P}_2^{[l]}$ are obtained as follows.

$\mathcal{P}_1^{[l]}$, $l = 0, \ldots, L_1$, is the unique solution to the following Lyapunov equation

$$\mathcal{A}_d^{[l]} \mathcal{P}_1^{[l]} \left(\mathcal{A}_d^{[l]} \right)^T - \mathcal{P}_1^{[l]} = - \left(\mathcal{W}^{[l]} + \mathcal{X}_\theta(t^{[l]}) \right) \left(\mathcal{W}^{[l]} + \mathcal{X}_\theta(t^{[l]}) \right)^T + \left(\mathcal{A}_d^{[l]} \right)^{J^{[l]}} \left(\mathcal{W}^{[l]} + \mathcal{X}_\theta(t^{[l]}) \right) \left(\mathcal{W}^{[l]} + \mathcal{X}_\theta(t^{[l]}) \right)^T \left(\left(\mathcal{A}_d^{[l]} \right)^{J^{[l]}} \right)^T$$

$\mathcal{P}_2^{[l]}$, $l = 0, \ldots, L_1$, is given by

$$\mathcal{P}_2^{[l]} = \left(I - \left(\mathcal{A}_d^{[l]} \right)^{J^{[l]}} \right) \left(I - \mathcal{A}_d^{[l]} \right)^{-1} \cdot \left(\mathcal{W}^{[l]} \left(\mathcal{W}^{[l]} \right)^T + \mathcal{X}_\theta(t^{[l]}) \left(\mathcal{W}^{[l]} \right)^T \right).$$

In the next section we illustrate the theoretical results presented in this section using an example from surface plasmon resonance experiments for the determination of the kinetic parameters of protein-protein interactions.

III. Biomedical Applications

Surface plasmon resonance (SPR) (see, e.g. [2], [6]) occurs under certain conditions from a conducting film at the interface between two media of different refractive index. Biosensors such as instruments by the BIAcore company offer a technique for monitoring protein-protein interactions in real time using an optical detection principle based on SPR. In the experiments one of the proteins (ligand) is coupled to a sensor chip and the second protein (analyte) is flowed across the surface coupled ligand using a micro-fluidic device. SPR response reflects a change in mass concentration at the detector surface as molecules bind or dissociate from the sensor chip. It can be used to estimate the kinetic constants of protein-protein interactions.

In this section we use the theoretical results presented in the previous section to analyze the SPR experiments for one-to-one protein-protein interactions that can be modeled by the differential equation

$$\dot{R}(t) = k_a \left(R_{max} - R(t) \right) C_0(t) - k_d R(t), t \geq t^{[0]}, R(t^{[0]}) = 0, \quad (11)$$

where $R(t)$ is the measured SPR response in resonance units (RU), k_a and k_d are the kinetic association and dissociation constants of the interaction respectively, R_{max} is the maximum analyte binding capacity in RU, $C_0(t)$ is the concentration value of the analyte in the flow cell which can be controlled in the experiments, and the initial SPR response is assumed to be zero.

Let $x_\theta(t) := R(t)$, $u(t) := C_0(t)$, $y_\theta(t) := R(t)$, $t \geq t^{[0]}$, and $x_0 := R(t^{[0]}) = 0$, (11) becomes the following bilinear system $\Phi = \{A, \ B, \ C, \ F_1\}$

$$\dot{x}_\theta(t) = A x_\theta(t) + F_1 u(t) x_\theta(t) + B u(t), \quad x_\theta(t^{[0]}) = x_0, \quad (12)$$

$$y_\theta(t) = C x_\theta(t), \quad t \geq t^{[0]}, \quad (13)$$

where $A = -k_d$, $B = k_a R_{max}$, $C = 1$, $F_1 = -k_a$. The unknown parameter vector to be estimated in the experiments is $\theta = \begin{bmatrix} k_a & k_d & R_{max} \end{bmatrix}^T$.

A practical SPR experiment may consist of an association phase ($t^{[0]} \leq t < t^{[1]}$) and a dissociation phase ($t^{[1]} \leq t < t^{[2]}$), or one of these two phases. During the association phase analyte is flowed across the ligand on the sensor chip with constant concentration C_0 up to time $t^{[1]}$, i.e., $C_0(t) = C_0, \ t^{[0]} \leq t < t^{[1]}$. The dissociation phase immediately follows the association phase and is characterized by analyte

free buffer being flowed across the sensor chip, i.e., $C_0(t) = 0,\ t^{[1]} \le t < t^{[2]}$. Hence, a two-phase SPR experiment can be modeled by the bilinear system $\Phi = \{A,\ B,\ C,\ F_1\}$ with a two-phase piecewise constant input

$$u(t) = u^{[0]}\beta_0(t) + u^{[1]}\beta_1(t), \quad t^{[0]} \le t < t^{[2]},$$

where $u^{[0]} = C_0, u^{[1]} = 0$ and $\beta_0(t)$, $\beta_1(t)$ are the indicators (see (4)). Note that in the two-phase SPR experiment the output samples are obtained from $y_\theta(t)$ for $t^{[0]} \le t < t^{[2]}$.

The first step is the calculation of the derivative system by Theorem 2.1. We represent the derivative system of $\Phi = \{A,\ B,\ C,\ F_1\}$ by $\Phi' = \{\mathcal{A},\ \mathcal{B},\ \mathcal{C},\ \mathcal{F}_1\}$ where $\mathcal{A}, \mathcal{B}, \mathcal{C}, \mathcal{F}_1$ are given as follows.

$\mathcal{A} :=$ diag $\{\partial_1 A,\ \partial_2 A,\ \partial_3 A\}$ where

$$\partial_1 A = \partial_3 A = \begin{bmatrix} -k_d & 0 \\ 0 & -k_d \end{bmatrix}, \quad \partial_2 A = \begin{bmatrix} -k_d & 0 \\ -1 & -k_d \end{bmatrix}.$$

$$\mathcal{B} := \begin{bmatrix} \partial_1 B \\ \partial_2 B \\ \partial_3 B \end{bmatrix} \text{ where } \partial_1 B = \begin{bmatrix} k_a R_{max} \\ R_{max} \end{bmatrix},$$

$$\partial_2 B = \begin{bmatrix} k_a R_{max} \\ 0 \end{bmatrix}, \quad \partial_3 B = \begin{bmatrix} k_a R_{max} \\ k_a \end{bmatrix}.$$

$\mathcal{C} :=$ diag $\{\partial_1 C_1,\ \partial_2 C_1,\ \partial_3 C_1\}$ where

$$\partial_1 C_1 = \partial_2 C_1 = \partial_3 C_1 = \begin{bmatrix} 0 & 1 \end{bmatrix}.$$

$\mathcal{F}_1 :=$ diag $\{\partial_1 F,\ \partial_2 F,\ \partial_3 F\}$ where

$$\partial_1 F_1 = \begin{bmatrix} -k_a & 0 \\ -1 & -k_a \end{bmatrix}, \quad \partial_2 F_1 = \partial_3 F_1 = \begin{bmatrix} -k_a & 0 \\ 0 & -k_a \end{bmatrix}.$$

Since the initial state x_0 of Φ is equal to zero, the initial state vector $\mathcal{X}_0$ of Φ' is also equal to zero.

The next step is to apply Theorem 2.2 to numerically calculate the CRLB. Here we use simulated data so that we could conveniently select various experimental settings. For comparison, typical numerical values from [6] are assigned to the unknown parameters, i.e.,

$$k_a = 1478\ \text{M}^{-1}\text{s}^{-1},\ k_d = 4.5 \times 10^{-3}\ \text{s}^{-1},\ R_{max} = 7.75\ \text{RU}.$$

The sampling intervals are chosen as $T_0 = T_1 = 1$ s, and the noise variance is assumed to be $\sigma^2 = 1$. Fig. 1 plots the CRLB in terms of the standard deviations of k_a, k_d and R_{max} as functions of C_0 and the number of data samples. Obviously, it shows that increasing the number of samples improves the accuracy of estimation. As can be seen from the figure, when the number of samples is sufficiently large, e.g. $J^{[0]} = J^{[1]} = 1000$, the CRLB approaches the asymptotic CRLB, which is the lowest possible CRLB, given fixed sampling intervals. The plot also reveals that the concentration value C_0 has an influence on the accuracy of parameter estimation. From Fig. 1(a), the optimal values of C_0 corresponding to the lowest variances of k_a for different number of data samples lie between 1.0×10^{-5} M and 2.0×10^{-5} M, and for C_0 greater than the optimal values the variance increases slowly with C_0. On the other hand, the variances of k_d and R_{max} decrease with the increase of C_0, but remain almost constant when C_0 is greater than 2.0×10^{-5} M. Therefore, a good choice of C_0 for practical two-phase SPR experiments would be around the value of 2.0×10^{-5} M .

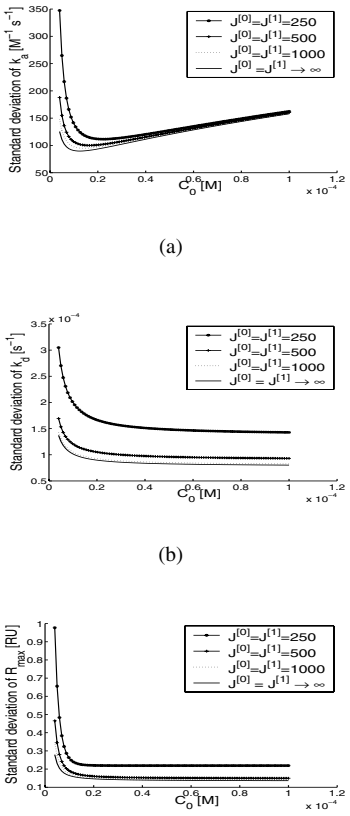

Fig. 1. The CRLB for simulated two-phase one-to-one SPR experimental data with $T_0 = T_1 = 1$ s and $\sigma^2 = 1$. (a), (b) and (c) plot the standard deviations of the estimates of k_a, k_d and R_{max} respectively for different concentration values and different numbers of samples acquired in the association and dissociation phases.

REFERENCES

[1] G. D. Baura, *System Theory and Practical Applications of Biomedical Signals*. New York: Wiley, 2001.

[2] R. Karlsson and A. Falt, "Experimental design for kinetic analysis of protein-protein interactions with surface plasmon resonance biosensors," *J. Immunol. Methods*, vol. 200, pp. 121–133, 1997.

[3] S. M. Kay, *Fundamentals of Statistical Signal Processing : Estimation Theory*. New Jersey: Prentice-Hall, 1993, vol. I.

[4] R. J. Ober, "The Fisher information matrix for linear systems," *Systems and Control Letters*, vol. 47, pp. 221–226, 2002.

[5] R. J. Ober, Q. Zou, and Z. Lin, "Calculation of the Fisher information matrix for multidimensional data sets," *IEEE Trans. Signal Processing*, vol. 51, pp. 2679–2691, Oct. 2003.

[6] R. J. Ober and E. S. Ward, "The influence of signal noise on the accuracy of kinetic constants measured by surface plasmon resonance experiments," *Anal. Biochem.*, vol. 273, pp. 49–59, 1999.

[7] R. R. Mohler, *Nonlinear systems, vol. II, Applications to Bilinear Control*. New Jersey: Prentice-Hall, 1991.

[8] Q. Zou, Z. Lin, and R. J. Ober, "The cramer rao lower bound for bilinear systems," *IEEE Trans. Signal Processing*, (submitted) 2004.