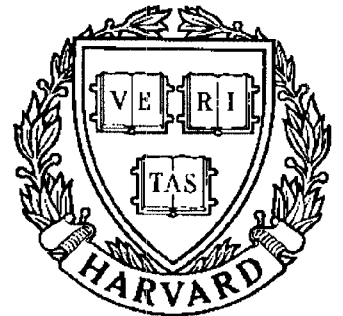


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**Minimum Mean Square Error Estimation of  
Connectivity in Biological Neural Networks**

*by X. Yang and S.A. Shamma*

# MINIMUM MEAN SQUARE ERROR ESTIMATION OF CONNECTIVITY IN BIOLOGICAL NEURAL NETWORKS

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**Abstract:** *A minimum mean square error (MMSE) estimation scheme is employed to identify the synaptic connectivity in neural networks. This new approach can substantially reduce the amount of data and the computational cost involved in the conventional correlation methods, and is suitable for both nonstationary and stationary neuronal firings. Two algorithms are proposed to estimate the synaptic connectivities recursively, one for nonlinear filtering, the other for linear filtering. In addition, the lower and upper bounds for the MMSE estimator are determined. It is shown that the estimators are consistent in quadratic mean. We also demonstrate that the conventional cross-interval histogram is an asymptotic linear MMSE estimator with an inappropriate initial value. Finally, simulations of both the nonlinear and linear (Kalman filter) estimates demonstrate that the true connectivity values are approached asymptotically.*

## 1 Introduction

The experimental identification of the topology of a neural network deals with the following question: Given a set of neural spike trains (or action potential processes), what can we say about the synaptic connectivity among the neurons recorded? The conventional method for accomplishing this task is to use correlation histograms, such as the cross-interval histogram, the cross-correlation histogram, the cross-covariance histogram and the joint post stimulus time (PST) histogram (Gerstein 1970; Habib and Sen 1985). Such a histogram is a linear estimate for the joint probability of firings of both presynaptic and postsynaptic neurons (Knox 1974; Brillinger 1975;

van den Boogaard et al. 1986; Yang and Shamma May 1990). A linear estimate needs sufficient observation data to assure its accuracy. However, besides the computational cost, a stable single unit recording usually lasts only for several minutes, making it difficult to collect sufficient data. Our objective in this report is to discuss alternative nonlinear estimates of the synaptic connectivity in biological neural networks.

Recently, several articles concerning the use of nonlinear methods for the correlation analysis have appeared in the literature. Borisyuk et al. (1985) presented a hazard procedure to extract the connectivity between neurons. Van den Boogaard (1986) used maximum likelihood (ML) estimation for a nonlinear self-exciting point process model (proposed by Ozaki (1979)) to study the feedback connectivity of a single neuron. Brillinger (1988) applied ML estimation in both continuous and discrete cases to analyze sea hare (*Aplysia californica*) data, where the transfer function of the neuron model was the standard normal distribution function. Finally, Chornoboy et al. (1988) employed the ML method to identify functional connectivities and to characterize neural interactions for linear neuron models.

To draw a statistical inference, it is essential to determine the bias, the consistency, and asymptotic behavior of the estimate. Under the assumption of stationarity, Ogata (1978) was able to show the asymptotic property of the ML estimation for point processes. The asymptotic behavior was also studied without assuming stationary conditions by Chornoboy et al. (1988) where the point process was decomposed into the sum of a predictable compensator and a zero-mean martingale, and Lengart's inequality was used to ensure the consistency of the ML method. However, this procedure was only successfully applied to a neuron model whose transfer function was linear. A linear neuron model can not be used to study inhibition because the intensity process (firing rate) is restricted to be nonnegative. Therefore, nonlinear estimation methods are necessary to study the connectivities in nonlinear neural network.

In this work, we focus on the minimum mean square error (MMSE) estimation method. Two recursive algorithm are developed to estimate the synaptic parameters by a nonlinear and a linear

(Kalman) filtering methods. An obvious advantage of the MMSE method is its unbiasedness. Although it is difficult in general to obtain the explicit expression of the MMSE for point process systems, we are able to obtain expressions of two lower bounds and an upper bound under some reasonable conditions. A comparison of the two lower bounds is also discussed. We prove that both nonlinear and linear MMSE estimators are consistent in quadratic mean by showing that the upper bound converges to zero. We also show that the linear MMSE estimation approaches the conventional cross-interval histogram estimates, with the advantage that it converges to the true value at a faster rate, and hence with less data required. All these issues are elaborated in section 3. Simulation results are given in section 4. All the proofs are contained in the appendix. For readers only interested in the implementation, algorithms 1 and 2 in subsections 3.2 and 3.3, respectively, are sufficient to serve as a manual. We begin our discussion in the next section with a description of the neuron model used in this study.

## 2 The Neuron Model and the Approach

The neuron model we use is the common model studied by Johannesma and van den Boogaard (1984), van den Boogaard et al. (1986), and Melssen and Epping (1987). The model and the estimation scheme is shown in Fig. 1, where  $\{T_1^A, T_2^A, \dots\}$  and  $\{T_1^B, T_2^B, \dots\}$  are the postsynaptic and presynaptic spike trains, respectively, and  $T_k^A, T_k^B$  represent the occurrence instant of the  $k$ -th spike in trains  $A$  and  $B$ .

The objective is to estimate the total effective synaptic connection  $h_X(t, s)$  which acts as a time-varying (in general) lowpass filter with constant parameters  $X = (W, \sigma)$ , where  $W$  is the connection strength, and  $\sigma$  is the integration time. Note that since there can be many synapses between any two neurons, it is impractical in modeling the neural network to account for individual synapses; rather, it is more fruitful both for experimental investigation and for mathematical description to consider the *total effective influence* of one neuron on another. The influence (on neuron  $A$ ) from other neurons (including self-excitation) is summarized as an unknown random component in the membrane potential which triggers a firing when it exceeds some threshold. Consequently, the

firing process can be adequately modeled as *doubly stochastic point process*. For further details, please refer to (Yang and Shamma May 1990), where in addition, the identification of connectivity among more than two neurons is also discussed.

The membrane potential  $V_t(X)$  is related to postsynaptic potential  $U_t = \sum_l h_X(t, T_l^B)$  via an invertible sigmoid mapping  $g(u)$ , i.e.,

$$V_t(X) = g\left(\sum_{l=1}^{N_B(t)} h_X(t, T_l^B)\right), \quad (1)$$

where  $N_B(t)$  is the spike count in train  $B$  in the observation interval  $(0, t]$ . An important observation here is that if the membrane potential ( $\{V_t(X) : t \geq 0\}$ ) and spike train  $B$  ( $\{T_l^B : l \geq 1\}$ ) are simultaneously observed by an intracellular recording of the postsynaptic neuron and an extracellular recording of the presynaptic neuron, then one can identify the connectivity via

$$g^{-1}(V_t) = \sum_{k=1}^{N_B(t)} h_X(t, T_k^B).$$

For example, suppose that the synapse is parametrized in the form known as a leaky integrator (Knox 1974):

$$h_X(t, s) = \begin{cases} We^{-(t-s)/\sigma}, & t \geq s \\ 0, & t < s \end{cases} \quad (2)$$

where  $W$  is the connection strength, and the time constant  $\sigma$  is small. They are treated as simple time-invariant random variables. Therefore, we have

$$g^{-1}(V_t) = W \sum_k e^{-(t-T_k^B)I(t \geq T_k^B)/\sigma} \simeq We^{-(t-T_t^B)/\sigma} \quad (3)$$

where  $T_t^B = \max\{T_l^B : T_l^B \leq t\}$  and  $I(\cdot)$  is an indication function. Then,  $W$  is estimated as

$$\hat{W} = g^{-1}(V_{T_l^B}), \quad l = 1, 2, \dots \quad (4)$$

Similarly, we have  $g^{-1}(V_{T_l^B+\Delta t}) \simeq W e^{-\Delta t/\sigma}$ , or

$$\hat{\sigma} = \left| \frac{\Delta t}{\ln(g^{-1}(V_{T_l^B})/g^{-1}(V_{T_l^B+\Delta t}))} \right| = \left| \frac{\Delta t}{\ln(\hat{W}/g^{-1}(V_{T_l^B+\Delta t}))} \right|, \quad l = 1, 2, \dots. \quad (5)$$

Unfortunately, such a simultaneous intracellular and extracellular recording is extremely difficult. In most practical situations, only simultaneous extracellular recordings of postsynaptic and presynaptic neurons are available. To make the above example work, we need first to estimate the membrane potential process  $\{V_t(X) : t \geq 0\}$ . There are two schemes to do it. One is to use a *hidden Markov model* (Yang and Shamma Jan. 1990), in which the optimization criterion is to maximize the joint probability of the observed spike train pattern and the estimated state path in the underlying Markov chain. The other uses the *minimum mean square error* estimation which we elaborate in this report.

### 3 The Minimum Mean Square Error Estimation

Denote by  $\{N_t^A : t \geq 0\}$  the counting process representing the spike pattern of neuron  $A$  (the postsynaptic neuron), and by  $\{N_t^B : t \geq 0\}$  the counting process representing that of neuron  $B$  (the presynaptic neuron). Note that they are associated with the point processes  $\{T_k^A : k \geq 1\}$  and  $\{T_k^B : k \geq 1\}$ , respectively. The physical meanings of these notations are stated in algorithm 1 in subsection 3.2.

#### 3.1 Nonlinear Filtering

The MMSE estimators are expressed as the conditional expectations of the parameters to be estimated, given the observed spike patterns of train  $A$  and  $B$ :

$$\hat{X}(t) = E[X | N_s^A, N_s^B : 0 \leq s < t] \quad (6)$$

where  $X = (W, \sigma)$ . Under a mild condition, namely, if the unknown random threshold (mentioned the second paragraph of section 2) has an exponential probability density function, then  $\{N_t^A :$

$t \geq 0$  is a doubly stochastic *Poisson* process. The Poisson process model has been discussed and its adequacy demonstrated in many situations (Correia and Landolt 1977; van den Boogaard et al. 1986). Hence, the conditional sample function density given the parameter  $X$  can be expressed as (Snyder 1975)

$$P_{N|X}(\{N_s^A : 0 \leq s < t\}|X) = \left[ \prod_{k=1}^{N_t^A} V_{T_k^A}(X) \right] e^{-\int_0^t V_\tau(X) d\tau} = e^{H_t(X)} \quad (7)$$

where

$$H_t(X) = -\int_0^t V_\tau(X) d\tau + \int_0^t \ln(V_\tau(X)) dN_\tau^A = -\int_0^t V_\tau(X) d\tau + \sum_{k=1}^{N_t^A} \ln(V_{T_k^A}(X)) \quad (8)$$

is a filtering process of  $V_t(X)$ , and  $\{V_t(X) : t \geq 0\}$  is the intensity process of the counting process  $\{N_t^A : t \geq 0\}$  representing the membrane potential of the postsynaptic neuron (see formula (1)). We will show that  $V_{T_k^A}(X)$  is a nonlinear function of the cross-interval between spike trains  $A$  and  $B$ , and all the correlation information is contained in  $H_t(X)$ . By Bayes' rule the MMSE estimator can be expressed as

$$\hat{X}(t) = \frac{E[X \exp\{H_t(X)\}]}{E[\exp\{H_t(X)\}]} \quad (9)$$

with the posterior probability density function of  $X$  as

$$P_{X|N}(x|N_s^A, N_s^B : 0 \leq s < t) = \frac{\exp\{H_t(x)\} P_X(x)}{E[\exp\{H_t(X)\}]} \quad (10)$$

where  $P_X(x)$  is the prior probability density function of  $X$ . Since we do not have any knowledge of  $X = (W, \sigma)$ ,  $W$  and  $\sigma$  are assumed to be uniformly distributed in  $[w_a, w_b]$  and  $(0, \sigma_b]$ , respectively. Therefore, (9) can be explicitly written as a nonlinear filtering form of

$$\bar{W}(t) = \frac{\int_{w_a}^{w_b} \int_0^{\sigma_b} w \exp\{H_t(w, \sigma)\} d\sigma dw}{\int_{w_a}^{w_b} \int_0^{\sigma_b} \exp\{H_t(w, \sigma)\} d\sigma dw} \quad (11)$$

and

$$\hat{\sigma}(t) = \frac{\int_{w_a}^{w_b} \int_0^{\sigma_b} \sigma \exp\{H_t(w, \sigma)\} d\sigma dw}{\int_{w_a}^{w_b} \int_0^{\sigma_b} \exp\{H_t(w, \sigma)\} d\sigma dw}. \quad (12)$$

### 3.2 Recursive Algorithms

Assume that the function  $V_t(\cdot)$  is known, i.e.,  $g(\cdot)$  in (1) is known. If we compute  $\hat{X}(t)$  at every  $t$ , the computational requirements become large as the observation time  $t$  increases. To avoid this, we propose a recursive algorithms for computing  $\hat{X}(t)$ . The idea is to create a look-up table storing the updated values of  $H_t(X)$  for different values of  $X$  in the distribution range. Then we make a recursive calculation for  $H_t(X)$  as

$$H_t(X) = H_s(X) - \int_s^t V_\tau(X) d\tau + \int_s^t \ln(V_\tau(X)) dN_\tau^A \quad (13)$$

with  $H_0(X) = 0$ , where

$$\int_s^t \ln(V_\tau(X)) dN_\tau^A = \sum_{k=N_s^A+1}^{N_t^A} \ln V_{T_k^A}(X). \quad (14)$$

Hence, the up-dating of the posterior density (10) is implemented using the up-dated  $H_t(X)$ . The above argument is summerized in the following algorithm.

*Algorithm 1.*

Step 0. Specify the function  $g(\cdot)$  in (1). For instance, a common assumption for  $g(\cdot)$  is a sigmoid function in (25). Specify an  $\epsilon$  - value as a criterion to terminate the algorithm when a satisfactory convergence is achieved. Have spike trains  $A$  and  $B$  ready.  $N_t^A$  and  $N_t^B$  are spike count up to time  $t$  in  $A$  and  $B$ ;  $T_l^A$  and  $T_l^B$  are the occurrence time of the  $l$ -th spike in  $A$  and  $B$ , respectively.

Step 1. Set  $s = 0$  and  $i = 1$ .



Step 2. Set  $t = i\Delta$ ; Use (13) and (14) to compute  $H_t(X)$  for different values of  $X = (W, \sigma)$  in the range  $W \in [w_a, w_b]$ ,  $\sigma \in (0, \sigma_b]$ .

Step 3. Use (11) and (12) to compute  $\hat{X}(t)$ .

Step 4. If  $|\hat{X}(t) - \hat{X}(s)| < \epsilon$ , stop. Otherwise, set  $s = t$ , increase  $i$  by 1, and goto 2.

### 3.3 Linear Filtering

If no assumptions about the function form for  $V_t(\cdot)$  are made, the following linear filtering and corresponding algorithm 2 can be used instead where only the average firing rate  $E[V_t]$  and its variance (or deviation)  $var(V_t)$  are known *a priori*. And they can be obtained from experiment, for instance,  $E[V_t]$  is an average firing rate usually estimated by averaging PST histograms.

Let us consider a *linear* MMSE estimator. It is known that the linear estimator of the intensity function for a point process  $\{N_t^A : t \geq 0\}$  can be written as (Macchi and Picinbono 1972)

$$\hat{V}_{lms}(t) = E[V_t(X)] + \int_0^t f(t, s)(dN_s^A - E[V_s(X)]ds), \quad (15)$$

where the linear filter  $f(t, s)$  is the solution of the following integral equation:

$$f(t, s)E[V_s(X)] + \int_0^t f(t, u)K_v(u, s)du = K_v(t, s), 0 \leq u \leq t, \quad (16)$$

where  $K_v(t, s)$  is the covariance function of the intensity process  $\{V_t(X) : t \geq 0\}$ . The resulting linear MMSE is

$$E[(\hat{V}_{lms}(t) - V_t)^2] = f(t, t) E[V_t(X)]. \quad (17)$$

As usual, it is difficult to solve the above integral equation. However, the design of filter  $f(t, s)$  depends only on the first and the second moments of  $\{V_t(X)\}$ . Hence one can construct another process model with the same  $K_v(t, s)$  and  $E[V_t(X)]$ , and come up with same filter  $f(t, s)$  and the same mean square error, regardless of the nature of process. This explains why the specific functional form of  $V_t(\cdot)$  is not necessary in linear MMSE estimation. Let us consider a process

$\{y_t\}$ , generated by the model

$$y_t = V_t + \sqrt{E[V_t]} w_t$$

where  $\{w_t\}$  is a zero-mean white noise process with variance 1, and is independent of  $\{V_t\}$ . It is not difficult to see that the process  $\{y_t\}$  has the same optimal linear  $f(t, s)$  for the estimation of  $\{V_t\}$  and the same mean square error. Furthermore, since the presynaptic spike pattern is known, we collect data  $\{y_t\}$  occurring only at  $t = T_l^B + \Delta t$ , ( $l = 1, 2, \dots$ ), at which the membrane potential does not depend on the integration time  $\sigma$ . Consequently,  $V(W) := V_{T_l^B + \Delta t}$  is a constant which depends only on the unknown  $W$ , for all  $l = 1, 2, \dots$ , and a Kalman filter can be used to estimate  $V$  (Srinath and Rajasekaran, 1979). The linear estimator in (15) can therefore be explicitly written as

$$\hat{V}_{lms}(T_l^B + \Delta t) = \hat{V}_{lms}(T_{l-1}^B + \Delta t) + \frac{\text{var}(V)}{E[V] + \text{var}(V)l\Delta t} (\Delta M_{T_l^B} - \hat{V}_{lms}(T_{l-1}^B + \Delta t)\Delta t), \quad l > 0 \quad (18)$$

with

$$\hat{V}_{lms}(T_l^B + \Delta t) = \hat{V}_{lms}(\Delta t) = E[V] + \frac{\text{var}(V)}{E[V]} (M_{\Delta t}), \quad l = 0;$$

or

$$\hat{V}_{lms}(T_l^B + \Delta t) = E[V] + \frac{\text{var}(V)}{E[V] + \text{var}(V)l\Delta t} (M_{T_l^B + \Delta t} - E[V]l\Delta t), \quad l = 0, 1, \dots \quad (19)$$

where  $\Delta t$  is the observing time bin and  $M_t$  is a cross-interval counting process:

$$M_t = \text{Number of spikes in } A \text{ immediately (within } \Delta t) \text{ following a spike in } B \quad (20)$$

with a correlation increment:

$$\Delta M_t = M_{t+\Delta t} - M_t = N_{t+\Delta t}^A - N_t^A, \quad \text{for } t = 0, T_1^B, T_2^B, \dots \quad (21)$$

The resulting MMSE is then given by

$$E[(\hat{V}_{lms}(t) - V)^2] = \frac{E[V] \cdot \text{var}(V)}{E[V] + \text{var}(V)N_t^B \Delta t}, \quad (22)$$

which can be obtained from the integral equation (16) as well. And it approaches 0 when  $t \rightarrow \infty$  — consistent in quadratic mean. Based on the above, we have the following

*Algorithm 2.*

Step 0. Assume that the average firing rate  $E[V]$  and its variance  $var(V_t)$  are estimated. For instance,  $E[V]$  can be estimated by the sample mean of a PST histogram of neuron  $A$  (i.e.,  $E[V] \simeq \int V_t dt$ ), and  $var(V)$  by the sample variance of the PST histogram (i.e.,  $var(V) \simeq \int V_t^2 dt - (\int V_t dt)^2$ ). Specify an  $\epsilon$  - value as a criterion to terminate the algorithm when a satisfactory convergence is achieved. Given spike trains  $A$  and  $B$ ,  $N_t^A$  is spike count up to time  $t$  in  $A$ , and  $T_l^B$  is the occurrence time of the  $l$ -th spike in  $B$ .

Step 1. Set  $l = 0$ .

Step 2. Set  $t = T_l^B$ . (Note  $T_0^B = 0$ ). Use (21) to determine  $\Delta M_t$  ( $= 1$ , if there is an A-spike in interval  $(t, t + \Delta t]$ ;  $= 0$ , otherwise).

Step 3. Use (18) or (19) to compute  $\hat{V}_{lms}(T_l^B + \Delta t)$ .

Step 4. If  $|\hat{V}_{lms}(T_l^B + \Delta t) - \hat{V}_{lms}(T_{l-1}^B + \Delta t)| < \epsilon$ , stop. Otherwise, increase  $l$  by 1, and goto 2.

One may decide that neuron  $B$  excites, or inhibits, or does not effect neuron  $A$  if the trend of  $\hat{V}_{lms}(T_l^B + \Delta t)$  is greater than, or less than, or close to  $E[V]$ . Moreover, if the function form  $V(\cdot)$  is available and invertible, then the estimate of  $W$ ,  $\hat{W}_{lms}$ , is uniquely determined by  $\hat{V}_{lms}$ .

### 3.4 Performance of the Estimates

The performance of an estimate is measured by its error and its asymptotic behavior. For the nonlinear MMSE estimation, the mean square error can not be explicitly analyzed. Instead, we shall discuss two lower bounds and an upper bound for the mean square error, as well as its consistency. The relation of the asymptotic behavior to the conventional cross-interval histograms is examined at the end of this subsection.

### 3.4.1 Lower Bounds

A usual lower bound for the mean square error is the Cramer-Rao (CR) bound which states that under some regularity assumptions, the MMSE of an estimator for  $W$  is bounded below by  $F^{-1}$ , i.e.,

$$E[(\hat{W} - W)^2] \geq F^{-1} \quad (23)$$

where  $F$  is the Fisher information defined as

$$F = E\left[\frac{\partial}{\partial w} \ln[P_{N|X}(\{N_s^A : 0 \leq s < t\}|W = w)P_X(x)]\right]^2. \quad (24)$$

The explicit analytic form of the Fisher information can be obtained if the following assumptions are used.

*Assumption 1.* Let us adopt a Boltzmann sigmoid function for the nonlinearity of the neuron:

$$g_t(u) = \alpha \frac{\beta_t e^u}{1 + \beta_t e^u}, \quad (25)$$

where  $\alpha$  is a deterministic positive constant, and  $\beta_t \geq 0$  for all  $t$ .

Clearly,  $\alpha$  acts as a spontaneous firing rate which can be estimated by measuring spontaneous firing rate ( $=\alpha\beta_t/1 + \beta_t$ ).  $\beta_t$  represents the effects of the refractory (or self-inhibiting) mechanisms. For instance, the absolute refractory effect of duration  $\delta$  can be modeled as  $\beta_t = 1 - I(t - T_t^A < \delta)$ , where  $I(E)$  is an indication function ( $I = 1$ , if  $E$  is true;  $I = 0$ , otherwise).

*Assumption 2.* The duration of the refractory effects is very small and hence is negligible. So  $\beta_t$  is a constant.

*Assumption 3.* For mathematical simplicity, we assume that the leaky integrator of the synapse of (2) is modified as

$$h_X(t, s) = WI(0 \leq t - s < \sigma), \quad (26)$$

and it depends only on the latest incoming spike (usually this is a dominating term) so that  $V_t(X) = g(h_X(t, T_t^B))$  where, again,  $T_t^B = \max\{T_l^B : T_l^B \leq t\}$ .

Note that these assumptions are made only to discuss the bounds for mean square error. They are independent of the algorithms discussed in subsections 3.2 and 3.3, although they could be used in algorithm 1 as a special case. Applying these assumptions here allows us to express the membrane potential at the occurrence instant of a postsynaptic spike as

$$V_{T_k^A}(X) = \alpha \frac{\beta e^{WI(T_k^A - T_{i_k}^B < \sigma)}}{1 + \beta e^{WI(T_k^A - T_{i_k}^B < \sigma)}}, \quad \forall k \quad (27)$$

where  $T_{i_k}^B = \max\{T_l^B : T_l^B \leq T_k^A\}$ . This is a nonlinear function of the cross-interval between spike trains  $A$  and  $B$  mentioned earlier. Based on the assumptions, we have propositions 1, 2, and 3 below; the proofs are given in the appendix.

*Proposition 1.* Under the conditions in assumptions 1, 2, and 3, the Fisher information for the MMSE of an estimator for  $W$  has the form of

$$F = \alpha \sum_{l=1}^{N_t^B} E\left[\frac{\beta e^W}{(1 + \beta e^W)^3} \min\{\sigma, (\min\{t, T_{l+1}^B\} - T_l^B)\} - E\left[\frac{\partial^2}{\partial w^2} \ln P_X(x)\right]\right]. \quad (28)$$

In particular, if  $W$  is uniformly distributed in  $[-w_b, w_b]$  and  $\sigma$  is an unknown constant, it follows that

$$F = \frac{\alpha(1 + \beta e^{w_b})^2 - (1 + \beta e^{-w_b})^2}{4w_b(1 + \beta e^{w_b})^2(1 + \beta e^{-w_b})^2} \sum_{l=1}^{N_t^B} \min\{\sigma, (\min\{t, T_{l+1}^B\} - T_l^B)\}. \quad (29)$$

Obviously,  $F^{-1} \rightarrow 0$  as  $t \rightarrow \infty$ . In some cases the CR bound can become trivial. Hero (1989) concluded, for example, that the CR bound is not tight for rapidly varying intensity functions. Therefore, he suggested using an information theoretic (IT) lower bound. An IT bound is related to the MMSE with the mutual information between a quantity and its estimate (Berger 1971).

*Proposition 2.* Under the conditions in assumptions 1, 2, and 3, the MMSE estimation of the synaptic strength  $W$  is bounded below by

$$E[(\hat{W} - W)^2] \geq \frac{1}{2\pi e} \exp\{2 \max\{h(W) - \alpha t + \int_0^t E[V_\tau(X)] d\tau, 0\}\} \quad (30)$$

where  $h(W)$  denotes the differential entropy of  $W$  defined as

$$h(W) = -E[\ln P_W(w)], \quad (31)$$

and

$$\int_0^t E[V_\tau(X)] d\tau = \frac{\alpha\beta}{1+\beta} \left\{ T_1^B + \sum_{i=1}^{N_t^B} \min\{(\min\{t, T_{i+1}^B\} - T_i^B), \sigma\} E\left[\frac{(1+\beta)e^W}{1+\beta e^W}\right] + \max\{(\min\{t, T_{i+1}^B\} - T_i^B - \sigma), 0\} \right\}. \quad (32)$$

A comparison can be made between the CR and IT bounds. We set  $\beta = 1$  for simplicity. First, if the firing rate of neuron  $B$  is low, then  $\sigma \leq \min(t, T_{i+1}^B) - T_i^B$ . The bounds are simplified as

$$CR = F^{-1} = \frac{4w_b}{\alpha\sigma N_t^B} \frac{(1+e^{w_b})^2(1+e^{-w_b})^2}{(1+e^{w_b})^2 - (1+e^{-w_b})^2}; \quad (33)$$

$$IT = \frac{2w_b^2}{\pi} e^{-(\alpha t + 1)}. \quad (34)$$

Note that  $h(W) = \ln(2w_b)$  and  $\ln((1+e^{w_b})/(1+e^{-w_b}))/w_b = 1$  are used in the derivation of the above IT bound. Next, if the firing rate of neuron  $B$  is high, then  $\sigma \geq \min(t, T_{i+1}^B) - T_i^B$ . The CR bound is simplified as

$$CR = F^{-1} = \frac{4w_b}{\alpha(t - T_1^B)} \frac{(1+e^{w_b})^2(1+e^{-w_b})^2}{(1+e^{w_b})^2 - (1+e^{-w_b})^2}, \quad (35)$$

where  $T_1^B$  (the instant of the first  $B$ -spike) is negligible. The IT bound remains the same. The CR bound in (33) can become that in (35) when neuron  $B$  fires stationarily with rate  $\mu_B = 1/\sigma$  so that  $\sigma N_t^B = \sigma \mu_B t = t$ . Both CR and IT bounds are shown in Fig. 2 together with an upper bound discussed next. They approach zero asymptotically. For small  $w_b$ , we have  $CR \leq IT$ , meaning that the CR bound is tighter than the IT bound (see Fig. 2 (a)). However, for large  $w_b$ , there is a

region of  $t$  in which the IT bound is tighter. This region is usually more practical since observation time  $t$  is moderate there (see Fig. 2(b)).

### 3.4.1 Upper Bound

A linear MMSE estimator is necessarily inferior to the nonlinear MMSE estimator of (9), and hence its error can be used as an upper bound. We can approximate the MMSE for  $W$  from the MMSE for  $V$  in (22) as follows.

*Proposition 3.* Under the conditions in assumption 1 and 2, the MMSE estimation of the synaptic strength  $W$  has an approximately asymptotic upper bound

$$E[(\hat{W}(t) - W)^2] \leq E[(\hat{W}_{lms}(t) - W)^2] \simeq \frac{(1 + \beta \exp(w_b \text{sgn}(\beta - 1)))^4}{(\alpha \beta \exp(w_b \text{sgn}(\beta - 1)))^2} \frac{E[V] \cdot \text{var}(V)}{E[V] + \text{var}(V) N_t^B \Delta t}. \quad (36)$$

Further,

$$\lim_{t \rightarrow \infty} E[(\hat{W}(t) - W)^2] \leq \lim_{t \rightarrow \infty} E[(\hat{W}_{lms}(t) - W)^2] = \frac{(1 + \beta \exp(w_b \text{sgn}(\beta - 1)))^4}{(\alpha \beta \exp(w_b \text{sgn}(\beta - 1)))^2} \lim_{t \rightarrow \infty} \frac{E[V]}{N_t^B \Delta t} = 0,$$

i.e., both MMSE estimators  $\hat{W}(t)$  and  $\hat{W}_{lms}(t)$  are consistent in quadratic mean.

### 3.4.3 Asymptotic Behavior of the Estimates vs. Cross-Interval Histograms

As summarized in proposition 3, the upper bound for the mean square error approaches zero, so does the mean square error itself. In addition, the asymptotic behavior of the linear MMSE estimate  $\hat{V}_{lms}(t)$  does not depend on the accuracy of  $E[V]$  and  $\text{var}(V)$ . In other words, a deviation in  $E[V]$  or/and  $\text{var}(V)$  will not effect  $\hat{V}_{lms}(t)$  when  $t$  is sufficiently large. To show this, we rewrite (19) as a function of  $\mu = E[V]$ :

$$\hat{V}_{lms}(T_l^B + \Delta t; \mu) = \mu + \frac{\text{var}(V)}{\mu + \text{var}(V) l \Delta t} (M_{T_l^B + \Delta t} - \mu l \Delta t).$$

Then a deviation of  $\mu$  results in

$$\hat{V}_{lms}(T_l^B + \Delta t; \mu + \delta) = \mu + \delta + \frac{\text{var}(V)}{\mu + \delta + \text{var}(V) l \Delta t} (M_{T_l^B + \Delta t} - (\mu - \delta) l \Delta t)$$

$$= \hat{V}_{lms}(T_l^B + \Delta t; \mu) \frac{\mu + \text{var}(V)l\Delta t}{\mu + \delta + \text{var}(V)l\Delta t} + \frac{\delta(2\mu + \delta)}{\mu + \delta + \text{var}(V)l\Delta t} \longrightarrow \hat{V}_{lms}(T_l^B + \Delta t; \mu)$$

as  $t$  (and hence  $l$ ) increases. A similar argument can be discussed for a deviation in  $\text{var}(V)$ . In fact, when  $t$  is sufficiently large, we have

$$\lim_{l \rightarrow \infty} \hat{V}_{lms}(T_l^B + \Delta t) = \lim_{l \rightarrow \infty} \frac{M_{T_l^B + \Delta t}}{l\Delta t}. \quad (37)$$

This limit does not depend on  $E[V]$  or  $\text{var}(V)$ . And this average cross-interval counting process  $M_{T_l^B + \Delta t}/l\Delta t$  is just the conventional cross-interval histogram valued at the first bin (bin width =  $\Delta t$ ) from the center. On the other hand, algorithm 2 with an initial  $\mu = E[V] = 0$  results in  $\hat{V}_{lms}(T_l^B + \Delta t; \mu)|_{\mu=0} = M_{T_l^B + \Delta t}/(l\Delta t)$ , becoming a cross-interval histogram. In conclusion, algorithm 2 estimates what cross-interval histograms estimate with the advantage that it converges faster (hence requires less data) at a cost of providing accurate  $E[V]$  and  $\text{var}(V)$  *a priori*; the cross-interval histograms are asymptotically the linear MMSE estimators with an erroneous initial value of  $E[V] = 0$  (meaning a zero average firing rate).

To extend the above, one can imagine that if  $\hat{V}_{lms}(T_l^B + \Delta t)$  estimates  $g(w)$ , then  $\hat{V}_{lms}(T_l^B + 2\Delta t)$  will estimate  $g(w \exp(-\Delta t/\sigma))$ , and  $\hat{V}_{lms}(T_l^B + k\Delta t)$  will estimate  $g(w \exp(-(k-1)\Delta t/\sigma))$ . To do so, just replace  $M_t$  in (19) with  $M_t^{(k)}$ :

$$M_t^{(k)} = \text{Number of spikes in } A \text{ following a spike in } B \text{ after } ((k-1)\Delta t, k\Delta t], \quad (38)$$

and repeat algorithm 2 for  $k = 1, 2, \dots, K+1$  to construct the right-half of a cross-interval histogram. Then interchange spike trains  $A$  and  $B$ , repeat the above to obtain the left-half. This generates a fast version of a cross-interval histogram. Further, as a by-product,  $\hat{\sigma}$  can be estimated (similar to (5)) as

$$\hat{\sigma}_{lms}(t)|_{t=T_l^B + \Delta t} = \frac{1}{K} \sum_{k=1}^K |\Delta t / \ln[g^{-1}(\hat{V}_{lms}(T_l^B + k\Delta t)) / g^{-1}(\hat{V}_{lms}(T_l^B + (k+1)\Delta t))]|. \quad (39)$$



## 4. Simulations and Discussions

To illustrate the nature of the estimates, we show the results from simulations of networks of both inhibitory and excitatory neurons. The neuron model used in the simulations is depicted in Fig. 1 where the sigmoid function is  $g(u) = \alpha e^u / (1 + e^u)$  (with  $\alpha = 10$ ). And the random threshold in the spike generator has an exponential distribution with variance 1. Figure 3 shows an inhibitory synaptic connection of (26) where the strength  $W = -0.5$  and the time constant  $\sigma = 12$  ms. Formula (11) is calculated using algorithm 1 with  $w_b = -w_a = 2$  and  $\sigma_b = 20$  ms. In addition, Kalman filtering is implemented using algorithm 2 with  $E[V] = \alpha/2$ ,  $var(V) = \alpha^2 \int_{w_a}^{w_b} (e^w / (1 + e^w))^2 dw - \alpha^2/4$ , and bin resolution  $\Delta t = 1$  ms. Figure 4 shows an excitatory connection of (2) where  $W = 0.3$  and  $\sigma = 6$  ms. In Fig. 5, formulas (12) and (39) are used to estimate the integration time  $\sigma$  with a synaptic connection of (2) where  $W = -0.8$  and  $\sigma = 4$  ms.

As shown in these figures, both Kalman filter and nonlinear estimates approach the true  $W$  and  $\sigma$  asymptotically, although Kalman filter estimates  $\hat{W}_{lms}(t)$  are inferior to the nonlinear estimates  $\hat{W}(t)$ . Note that although the form of the synaptic connection in Fig. 3 is different from that in Figs. 4 and 5, the Kalman estimates perform uniformly well without any corresponding changes. This supports the notion that Kalman filtering can be used in general regardless the detail of the synaptic connection. In contrast to the conventional linear correlation histogram in which minutes of data are required for the estimation, the MMSE estimation in these simulations need only 10 seconds of data with an acceptable accuracy.

## Acknowledgments

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## Appendix

*Proof of Proposition 1:* For fixed  $t$ , we see that

$$\int_0^t E\left\{\left[\frac{\partial}{\partial w} \ln V_\tau(x)\right]^2 V_\tau(x)\right\} d\tau < t < \infty,$$

since  $V_t(x) < 1$  and  $\partial \ln V_t(x)/\partial w < 1$ . It follows that (Hero 1989, proposition 1)

$$F = \int_0^t E\left\{\left[\frac{\partial}{\partial w} \ln V_\tau(x)\right]^2 V_\tau(x)\right\} d\tau + E\left[\frac{\partial}{\partial w} \ln P_X(x)\right]^2. \quad (40)$$

Because  $(\partial \ln V_t(x)/\partial w)^2 V_t(x) = \alpha I(t - T_t^B \leq \sigma) \beta_t e^{wI(t - T_t^B \leq \sigma)} / (1 + \beta_t e^{wI(t - T_t^B \leq \sigma)})^3$ , the first term in Fisher information becomes

$$E\left\{\int_0^t \left[\frac{\partial}{\partial w} \ln V_\tau(x)\right]^2 V_\tau(x) d\tau\right\} = E\left\{\alpha \sum_{l=1}^{N_t^B} \int_{T_l^B}^{\min\{T_l^B + \sigma, \min\{T_{l+1}^B, t\}\}} \frac{\beta(l) e^W}{(1 + \beta(l) e^W)^3} d\tau\right\}, \quad (41)$$

which is the first term in (28). For the second term, it is shown that (Srinath and Rajasekaran 1979))

$$E\left[\frac{\partial}{\partial w} \ln P_X(x)\right]^2 = -E\left[\frac{\partial^2}{\partial w^2} \ln P_X(x)\right],$$

which completes the proof.

*Proof of Proposition 2:* Let us start with a distortion-rate function (Berger 1971) defined as

$$D(R) = \min_{P(\hat{w}|w) \in \mathcal{P}} E[(\hat{W} - W)^2] \quad (42)$$

where  $\mathcal{P}$  is the set of transition probabilities  $P(\hat{w}|w)$  for all estimation schemes, for a given  $P_X(x)$ , with the property that the mutual information does not exceed a given constant  $R$ , namely,

$$\mathcal{P} = \{P(\hat{w}|w) : I(\hat{W}; W) \leq R\}.$$

And

$$D(R) \geq D_L(R) = \frac{1}{2\pi e} e^{2h(W)} e^{-2R},$$

where  $D_L(R)$  is known as Shannon lower bound. Because the minimum in (42) is achieved at the boundary of  $\mathcal{P}$ , it follows that

$$E[(\hat{W} - W)^2] \geq \frac{1}{2\pi e} e^{2h(W)} e^{-2I(\hat{W}; W)}.$$

It is obvious that  $I(\hat{W}; W) \leq I(N; W)$ , because  $\hat{W}$  is a function of  $\{N_s^A : 0 \leq s < t\}$ .

To complete the proof, it suffices show that

$$I(N; W) \leq \min\{h(W), \alpha t - \int_0^t E[V_\tau(X)] d\tau\} \quad (43)$$

where  $\int_0^t E[V_\tau(X)] d\tau$  is expressed in (32).

First, it is known that  $I(N; W) \leq h(W)$ . Next, we show that  $I(N; W) \leq \alpha t - \int_0^t E[V_\tau(X)] d\tau$ .

By definition, we have

$$I(N; W) = E\left[\ln\left(\frac{P_{N|W}(\{N_s^A : 0 \leq s < t\}|W)}{P_N(\{N_s^A : 0 \leq s < t\})}\right)\right]. \quad (44)$$

From (7) and (8), the numerator becomes

$$E[\ln(P_{N|W}(\{N_s^A : 0 \leq s < t\}|W))] = \int_0^t E[\ln(V_\tau(X)) V_\tau(X)] d\tau - \int_0^t E[V_\tau(X)] d\tau. \quad (45)$$

Then the denominator is lower bounded by

$$\begin{aligned} E\{\ln(P_N(\{N_s^A : 0 \leq s < t\}))\} &= E\{\ln(E[e^{-\int_0^t V_\tau(X) d\tau} \prod_{k=1}^{N_t^A} V_{T_k^A}(X)])\} \\ &\geq E\{\ln(E[e^{-\alpha t} \prod_{k=1}^{N_t^A} V_{T_k^A}(X)])\} = -\alpha t + E\{\ln(E[\prod_{k=1}^{N_t^A} V_{T_k^A}(X)])\} \\ &\geq -\alpha t + E\{E[\ln(\prod_{k=1}^{N_t^A} V_{T_k^A}(X))]\} = -\alpha t + \int_0^t E\{[\ln(V_\tau(X))] V_\tau(X)\} d\tau. \end{aligned} \quad (46)$$

To get the first inequality, the fact that  $V_t(X) < 1$  was used; to get the second inequality, Jensen's inequality  $\ln(EV) \geq E(\ln V)$  was played. The last equality was obtained by the fact that  $E[\sum_{k=1}^{N_t^A} g(T_k^A, X)] = \int_0^t E[g(\tau, X) V_\tau(X)] d\tau$  (see (Larson and Shubert 1979, p.635) for a proof).

Combining (44), (45), and (46), we obtain (43). And (32) follows that

$$\int_0^t E[V_\tau(X)] d\tau = E\left[\sum_{l=1}^{N_t^B} \int_{T_l^B}^{\min\{T_l^B + \sigma, \min\{t, T_{l+1}^B\}\}} \frac{\alpha\beta e^W}{1 + \beta e^W} d\tau\right].$$

*Proof of Proposition 3:* We express  $w = g^{-1}(v) = \ln(v/(\alpha - v)) - \ln\beta$  in a Talor form as  $w = g^{-1}(v_0) + dg^{-1}(v)/dv|_{v=\xi}(v - v_0)$ , where  $\xi$  satisfies  $v_0 \leq \xi \leq v$  (or  $v \leq \xi \leq v_0$ ), and  $v_0$  corresponds to  $w = 0$ . Therefore, for  $0 \leq \lambda \leq 1$  we have

$$\begin{aligned} E[(\hat{W}_{lms}(t) - W)^2] &= E\left[\frac{(1 + \beta \exp(\lambda W))^4}{(\alpha\beta \exp(\lambda W))^2} (\hat{V}_{lms}(t) - V)^2\right] \\ &\leq \frac{(1 + \beta \exp(w_b \operatorname{sgn}(\beta - 1)))^4}{(\alpha\beta \exp(w_b \operatorname{sgn}(\beta - 1)))^2} E[(\hat{V}_{lms}(t) - V)^2]. \end{aligned}$$

Then, applying (22) completes the proof.

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Figure 1: The Neuron Model and the Estimation Scheme.

Figure 2: A Comparison of the CR and IT Bounds. (a) The two lower bounds (34) and (35) and the upper bound (36) are plotted against  $\alpha t$  where  $w_b = -w_a = 2.5$ . Also  $N_t^B = E[V]t$  and  $\beta = 1$ . The CR bound is always tighter than the IT bound in this case. (b) The two lower bounds (34) and (35) are plotted against  $\alpha t$  where  $w_b = -w_a = 64$ . In this case, the IT bound is tighter than the CR bound in the region  $[0.45, 1.95]$ .

Figure 3: Estimation of the Connection strength. Results from the simulation of an inhibition neural network of Fig. 1, where the synaptic connectivity has a form of (26) where the connection strength  $w = -0.5$  and the integration time  $\sigma = 12 \text{ ms}$ .

Figure 4: Estimation of the Connection strength. Results from the simulation of an excitatory neural network of Fig. 1, where the synaptic connectivity has a form of (2) where the connection strength  $w = 0.3$  and the integration time  $\sigma = 6 \text{ ms}$ .

Figure 5: Estimation of the Integration Time. Results from the simulation of an inhibition neural network of Fig. 1, where the synaptic connectivity has a form of (2) where the connection strength  $w = -0.8$  and the integration time  $\sigma = 4 \text{ ms}$ .

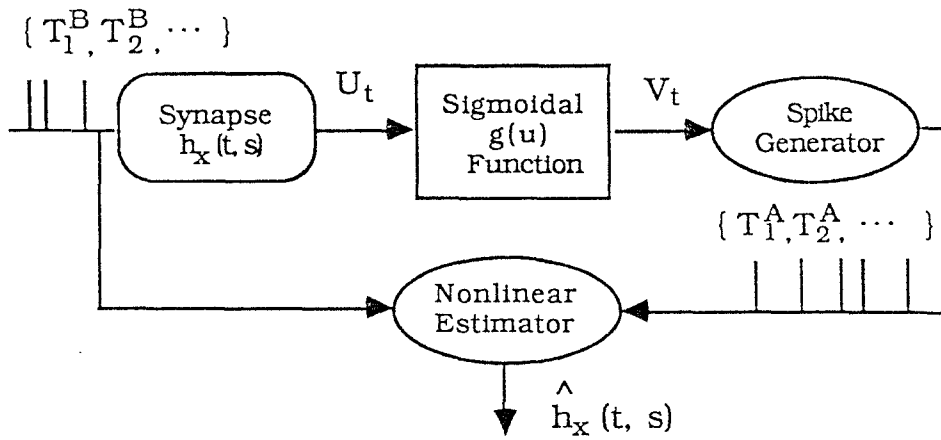


Figure 1

Figure 1: The Neuron Model and the Estimation Scheme

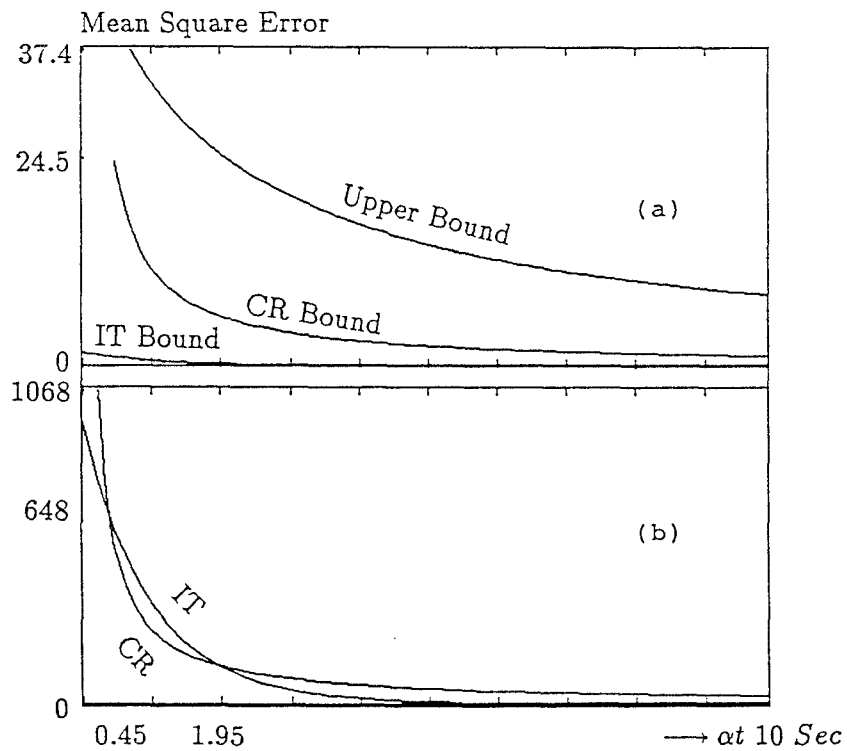


Figure 2



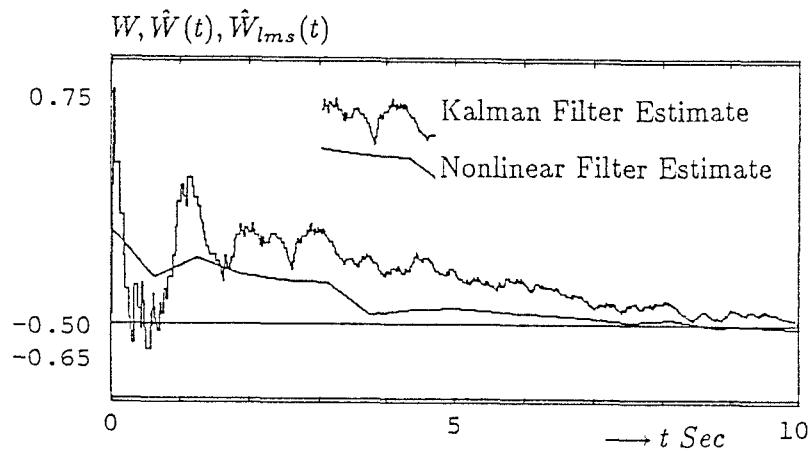


Figure 3

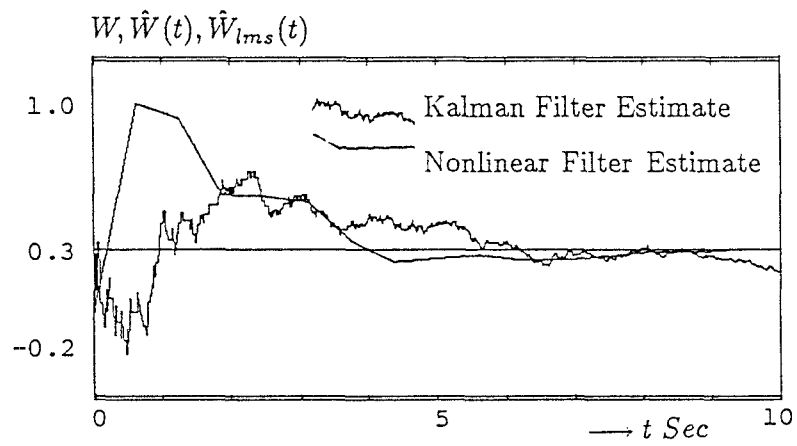


Figure 4

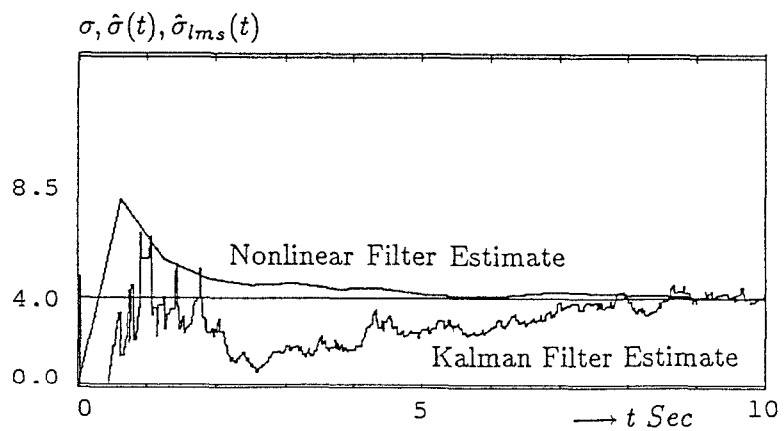


Figure 5