33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

A dual Kalman filter for parameter-state estimation in real-time DNA microarrays

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***Abstract*—Affinity-based biosensors rely on chemical attraction between analytes (targets) and their molecular complements (probes) to detect presence and quantify amounts of the analytes of interest. Real-time DNA microarrays acquire multiple temporal samples of the target-probe binding process. In this paper, estimation of the amount of targets based on early kinetics of the binding reaction is studied. A dual Kalman filter for the parameter-state estimation is proposed. Computational studies demonstrate efficacy of the proposed method.**

Index Terms: DNA microarrays, real-time, dual Kalman filter

I. Introduction

Detecting and quantifying the presence amounts of various nucleic acid sequences (DNA,mRNA, microRNA) is an important problem in genomics [1]-[2]. DNA microarrays sense interaction between target nucleic acid sequences and biological sensing elements, and generate signal proportional to the amount of target molecule. The chemical attraction between the two leads to binding process in which probes capture target analytes. There are different transduction methods for counting the binding events, e.g., fluorescence, electrochemical, etc. Several thousands of different analytes can be detected simultaneously due to parallelization of the process. Thus these systems are both time and cost efficient and may enable exciting new applications in drug discovery, medicine, defense systems, and environmental monitoring. But some of the shortcomings of this technology are that detection is subject to interference, noise, probe saturation, and other sources of errors in the analyte detection procedure [3]-[4]. This adversely affects the sensitivity, dynamic range and resolution of the DNA microarrays. An important impediment is that the binding process is a stochastic process which the conventional microarrays attempt to characterize based on a single sample from the steady state distribution. As an alternative one could estimate the amount of target analytes by obtaining temporal sampled kinetics of the binding process. This is expected to improve both accuracy and response time [5].

II. Mathematical model

Consider a DNA microarray with N different types of probes on its surface. Each probe is designed to capture one of the targets possibly present in a biological sample that is to be tested. Let M denote the actual number of different target types that are present in the sample, $M \leq N$. The real-time DNA microarrays acquire temporal samples of the binding process, i.e., they provide a time-series of the number of captured target molecules collected at discrete points in time. Note that in addition to hybridization to its matching probe, a target molecule may also engage in non-specific cross-hybridization with probes whose nucleotide sequences are only partial matches with the target. We assume that, in general, the i^{th} target may hybridize to its corresponding specific probe as well as cross-hybridize to $C_i \leq N-1$ non-specific ones. Both hybridization and cross-hybridization are treated as random events. The probabilities of specific and non-specific binding of the i^{th} target to the i^{th} and j^{th} probe are denoted by p_{ii} and p_{ij}, respectively. On the other hand, if all we have in the system is binding (i.e., hybridization and cross-hybridization) then, if enough probes are present, eventually all target molecules would bind to the probes. However, this is not the case since both hybridization and cross-hybridization are reversible processes: once a target molecule is bound to a probe there is a nonzero probability that it will be released. We denote the release probability from the hybridized and cross-hybridized state by p^r_{ii} and p^r_{ij} , respectively.

We use the following notation

- $n_i(t)$: the number of free targets of type i at time t
- $n_{b,ij}(t)$: the number of targets of type i bound to the probe j at time t
- $n_{b,j}(t)$: the total number of targets of all types captured by the probe j.

The desired parameter is $n_i(0)$, the total number of target molecules of type i in the biological sample being tested. Moreover it holds that $n_i(t) = n_i(0) - \sum_j n_{b,ij}(t)$.

Assume the realistic scenario where the number of target molecules is much smaller than the number of probe molecules. In other words that there is no saturation of the probes. Then the change in the number of target molecules of type i bound to the probe molecules of type j in the time interval $(t, t+\Delta)$ is given by $n_{b,ij}(t+\Delta) - n_{b,ij}(t) = (n_i(0) - \sum_{j'} n_{b,ij'}(t))p_{ij} - n_{b,ij}p^r_{ij}$. Now, the binding probability p_{ij} is affected by the capturing process- the fewer available (i.e., unbound) probes, the less likely that a free target will be captured. Let π_{ij} denote the probability of a target molecule of type i being captured by the probe j when the number of probe molecules is unlimited. Then the probability π_{ij} in $(t, t+\Delta)$ can be found as $p_{ij} = \pi_{ij}(n_p - \sum_{i'} n_{b,i'j}(t))/n_p$, where n_p denotes the number of probe molecules. Therefore we can write

$$n_{b,ij}(t+\Delta) - n_{b,ij}(t)$$
$$= \left(n_i(0) - \sum_{j'} n_{b,ij'}(t)\right)\left(1 - \frac{\sum_{i'} n_{b,i'j}(t)}{n_p}\right)\pi_{ij} - n_{b,ij}p^r_{ij}$$

This work was supported by the National Science Foundation under grant CCF-0845730.

By dividing both sides with Δ and letting $\Delta \to 0$, we obtain

$$\frac{dn_{b,ij}}{dt} = \Big(n_i(0) - \sum_{j'} n_{b,ij'}(t)\Big)\left(1 - \frac{\sum_{i'} n_{b,i'j}(t)}{n_p}\right)k_{ij} - n_{b,ij}k^r_{ij} + w_{ij}(t) \quad (1)$$

where k_{ij} and k^r_{ij} denote the forward and backward reaction rate of the binding and disassociation process, respectively, and where we introduce w_{ij} to model the uncertainty of the sensing process. The random variables w_{ij} are assumed to be zero-mean Gaussian with variance proportional to $n_{b,ij}$, i.e., the uncertainty has shot-noise characteristics. We focus on the early part of the reaction where $\sum_{j'} n_{b,ij'}(t) << n_i(0) << n_p$. Here we ignore the quadratic terms in (1), and after rearranging obtain

$$\frac{dn_{b,ij}}{dt} = -\left(\sum_{j'} n_{b,ij'}(t) + \frac{n_i(0)}{n_p}\sum_{i'} n_{b,i'j}(t)\right)k_{ij} - n_{b,ij}(t)k^r_{ij} + n_i(0)k_{ij} + w_{ij}(t) \quad (2)$$

For convenience, denote $\mathbf{x}_i = [n_{b,i1}\ n_{b,i2} \dots n_{b,iN}]^T, 1 \le i \le M$ and $\mathbf{x} = [\mathbf{x}_1\ \mathbf{x}_2 \dots \mathbf{x}_M]^t$. So $\mathbf{x}$ is an $MN-$ dimensional vector comprising of M target types bound to each of the N probes. Let $\mathbf{k}_i = [k_{i1}\ k_{i2} \dots k_{iN}]^T$, and $\mathbf{k}^r_i = [k^r_{i1}\ k^r_{i2} \dots k^r_{iN}]^T$. Moreover, let $D_{\mathbf{k}} = \text{diag}\big(\mathbf{k}_1, \mathbf{k}_2, \dots, \mathbf{k}_M\big)$, and $D_{\mathbf{k^r}} = \text{diag}\big(\mathbf{k}^r_1, \mathbf{k}^r_2, \dots, \mathbf{k}^r_M\big)$, i.e., $D_{\mathbf{k}}$ and $D_{\mathbf{k^r}}$ are diagonal matrices are diagonal matrices having k_{ij} and k^r_{ij} as the diagonal entries, respectively. Then we can write (2) as the following SDE

$$\frac{d\mathbf{x}}{dt} = \mathbf{b} - A\mathbf{x} + \mathbf{w} \quad (3)$$

where the $MN-$ dimensional vectors $\mathbf{b}$ and $\mathbf{w}$ are defined as

$$\mathbf{b} = \begin{bmatrix} n_1(0)\mathbf{k}_1 \\ \cdot \\ \cdot \\ n_M(0)\mathbf{k}_M \end{bmatrix}, \quad \mathbf{w} = \begin{bmatrix} w_{11} \\ \cdot \\ \cdot \\ w_{MN} \end{bmatrix}$$

and where $A = D_{\mathbf{k^r}} + D_{\mathbf{k}}[(\mathbf{1}\mathbf{1}^{'}) \otimes I] + \frac{1}{n_p}D_{\mathbf{b}}[I \otimes (\mathbf{1}\mathbf{1}')]$. Note that the number of target molecules captured by each of the probes can be expressed as

$$\begin{bmatrix} n_{b,1}(t) \\ \cdot \\ \cdot \\ n_{b,N}(t) \end{bmatrix} = \begin{bmatrix} \sum_i n_{b,i1}(t) \\ \cdot \\ \cdot \\ \sum_i n_{b,iN}(t) \end{bmatrix} = H\mathbf{x}(t)$$

where the dimension of $H = [I_N\ \ I_N\ \ \dots I_N]$ is $N \times MN$. The noisy measured process is thus given by $\mathbf{y}_t = \rho H\mathbf{x}(t) + \mathbf{v}(t)$ where ρ denotes the transduction coefficient mapping the number of molecules to light intensities and $\mathbf{v}(t)$ is the Gaussian measurement noise of variance σ^2_v. The continuous time measurement model and the SDE model is thus given

$$\frac{d\mathbf{x}}{dt} = \mathbf{b} - A\mathbf{x} + \mathbf{w}, \quad \mathbf{y}_t = \rho H\mathbf{x}(t) + \mathbf{v}(t) \quad (4)$$

III. Discretized Model

The solution to the SDE model (3) is given by

$$\mathbf{x}(t) = \Big(I - e^{-At}\Big)A^{-1}\mathbf{b} + \int_0^t e^{-A(t-\tau)}\mathbf{w}(\tau)d\tau \quad (5)$$

The continuous time state space model for the process is given by

$$\mathbf{x}(t+\tau) = \Big(I - e^{-A\tau}\Big)A^{-1}\mathbf{b} + e^{-A\tau}\mathbf{x}(t) + \boldsymbol{\epsilon}(t,\tau) \quad (6)$$

where $\boldsymbol{\epsilon}(t,\tau) = \int_t^{t+\tau} e^{A(u-\tau)}d\mathbf{w}(u)$. The discretized SDE model (4) is thus given by (under the assumption of sufficiently fast sampling) is given by

$$\mathbf{x}(t+\tau) = \tau\mathbf{b} + (I - A\tau)\mathbf{x}(t) + \underbrace{\int_t^{t+\tau}\Big(I + A(u-\tau)\Big)d\mathbf{w}(u)}_{I(t,\tau)} \quad (7)$$

The integral in (7) can be simplified as

$$I(t,\tau) = \Big(I - A\tau\Big)\mathcal{N}\Big(0, \tau D_{\mathbf{b}\tau}\Big) + A\mathcal{N}\Big(0, \frac{(t+\tau)^3 - t^3}{3}D_{\mathbf{b}\tau}\Big)$$

where the covariance matrix of $\mathbf{w}$, $R_{\mathbf{w}}(\tau) = D_{\left(I - e^{-A\tau}\right)A^{-1}\mathbf{b}}$ If the discrete samples of the observations are obtained at $k\Delta, k = 1, 2, \dots, L$, the discrete equivalent model to (4) is given by

$$\begin{aligned} \mathbf{x}_{k+1} &= \mathbf{b}\Delta + (I - A\Delta)\mathbf{x}_k + \mathbf{z}_k \\ \mathbf{y}_k &= \rho H\mathbf{x}_k + \mathbf{v}_k \end{aligned} \quad (8)$$

where $\mathbf{x}_k = \mathbf{x}(k\Delta)$, $\mathbf{y}_k = \mathbf{y}(k\Delta)$, $\mathbf{v}_k = \mathbf{v}(k\Delta)$, $E\Big[\mathbf{v}_k\mathbf{v}_l^{'}\Big] = \sigma^2_v I_N \delta_{kl}$.

$$z_k \sim \Big(I - A\Delta\Big)\mathcal{N}\Big(0, \Delta D_{\mathbf{b}\boldsymbol{\Delta}}\Big) + A\mathcal{N}\Big(0, D_{\mathbf{b}\boldsymbol{\Delta}}\Delta^3\frac{3k^2+3k+1}{3}\Big)$$

$$E\Big[\mathbf{z}_k\mathbf{z}_l^{'}\Big] = R_z(k,l) = \Bigg(\Delta\Big(I - A\Delta\Big)D_{\mathbf{b}\boldsymbol{\Delta}}\Big(I - A\Delta\Big)^T + AD_{\mathbf{b}\boldsymbol{\Delta}}A^T\Delta^3\frac{3k^2+3k+1}{3}\Bigg)\delta_{kl} \quad (9)$$

The SDE model (4) is the so-called multivariate Ornstein-Uhlenbeck (O-U) process which is popular approach to model interest rates, currency exchange rates, and commodity prices stochastically. The Ornstein-Uhlenbeck process, also known as the Vasicek model, is the continuous-time analogue of the discrete-time AR(1) process [6]. The measured process in (8) is thus a partially observed discrete samples of a multivariate Ornstein-Uhlenbeck (O-U) process. We are interested in estimating the amounts of targets $\boldsymbol{\theta} = [n_1(0),\ n_2(0)\ \dots, n_M(0)]^T$ from the observations $\{\mathbf{y}_k\}$. Note that the vector $\mathbf{b}$ and matrix A are parameter dependent. The discrete state space model (8) is a linear model, with the transfer matrix $(I - A\Delta)$ depending on the desired parameters $\{n_i(0)\}$. Further the state dynamic noise $\mathbf{z}_k$ is also parameter dependent. The problem of estimating the amount of analytes of different types given the discrete observations $\mathbf{y}_k,\ 1 \le k \le L$ can thus be formulated as joint state-parameter estimation of

the state space model (8). Some popularly employed non-linear estimation techniques [7] include sigma-point particle filter, UKF, EKF etc. The efficiency of these techniques are many a times are application dependent. In the present application, the state-space model is bilinear and this can be exploited to implement simple estimation technique. In this work, we propose to tackle the joint state parameter estimation problem using an iterative procedure based on dual Kalman filtering [8]. The proposed approach is motivated as follows. On one hand, given the true values of the parameters, the state space model in (8) corresponds to linear model. On the other hand, given the true values of the states, we can interpret the state space model as a linear model in the desired parameters. Hence we can use two Kalman filters in parallel; One Kalman filter is used to estimate the states given an estimate of the parameters and another Kalman filter to estimate the parameters given an estimate of the states. We iterate between these two Kalman filters until convergence.

IV. The Dual Kalman filter

In this section, we provide the dual Kalman filtering approach for joint state parameter estimation. Let us first rewrite the state dynamics in (8) in terms of the parameters θ as follows, $\mathbf{x}_{n+1} = \left(\Delta G_k - \frac{1}{n_p}[H\mathbf{x}_n \otimes I]\right)^t \boldsymbol{\theta}_k + \Big(I - \big(D_{\mathbf{k}_r} + D_{\mathbf{k}}[(\mathbf{1}\mathbf{1}^T) \otimes I]\big)\Big)\mathbf{x}_n + \mathbf{z}_n(\theta_k)$.

Hence, we can write a (pseudo) linear observation model for the parameters $\boldsymbol{\theta}$ as follows

$$\tilde{\mathbf{y}}_n \quad = \quad \left(\Delta G_k - \frac{1}{n_p}[H\mathbf{x}_n \otimes I]\right)^t \boldsymbol{\theta} + \mathbf{z}_n(\theta_k)$$

where $\tilde{\mathbf{y}}_n \stackrel{\text{def}}{=} \mathbf{x}_{n+1} - \Big(I - \big(D_{\mathbf{k}_r} + D_{\mathbf{k}}[(\mathbf{1}\mathbf{1}^T) \otimes I]\big)\Big)\mathbf{x}_n$

$$G_k = \begin{bmatrix} \mathbf{k}_1 & \mathbf{0} & \dots & \mathbf{0} \\ \mathbf{0} & \mathbf{k}_2 & \dots & \mathbf{0} \\ \dots & \dots & \dots & \dots \\ \mathbf{0} & \mathbf{0} & \dots & \mathbf{k}_M \end{bmatrix}$$

A. Kalman filtering for estimating state sequence

For a fixed parameter set $\hat{\boldsymbol{\theta}}$, we use the linear state space model in (8). Hence the state estimates obtained using a Kalman filter is optimal in the sense of minimizing the mean square error. The Kalman filtering as applied to the state space model for a fixed parameter is summarized in Algorithm 1.

The optimal states estimates $\hat{\mathbf{x}}_n$ in Algorithm (1) forms a input to update the estimate of the parameter which is discussed in the next section.

B. Kalman filtering for estimating parameters

Using the state estimates $\hat{\mathbf{x}}_n$, the pseudo observation model (10) becomes

$$\begin{aligned} \hat{\mathbf{y}}_n &= F_{11}(n)\boldsymbol{\theta} + F_{12}(\boldsymbol{\theta})\mathcal{N}\Big(0, \Delta D_{\mathbf{b}\boldsymbol{\Delta}}\Big) \\ &+ A(\boldsymbol{\theta})\mathcal{N}\Big(0, \Delta^3 D_{\mathbf{b}\boldsymbol{\Delta}} \frac{3n^2+3n+1}{3}\Big) \end{aligned} \qquad (10)$$

Algorithm 1 Kalman filtering: State estimation

1. Initialization: $\hat{\mathbf{x}}_{0|0}, \ P_{0|0}$.
for n=1 to L **do**
2a. Prediction:

$$\begin{aligned} \hat{\mathbf{x}}_{n|n-1} &= \mathbf{b}\Delta + \big(I - A\Delta\big)\hat{\mathbf{x}}_{n-1|n-1} \\ P_{n|n-1} &= \big(I - A\Delta\big)P_{n-1|n-1}\big(I - A\Delta\big)^T + R_z(n,n) \\ \hat{\mathbf{e}}_n &= \mathbf{y}_n - H\hat{\mathbf{x}}_{n|n-1} \end{aligned}$$

2b. Filtering:

$$\begin{aligned} K_n &= P_{n|n-1}H_n^T\Big(HP_{n|n-1}H^T + \sigma_{\mathbf{v}}^2 I\Big)^{-1} \\ \hat{\mathbf{x}}_{n|n} &= \hat{\mathbf{x}}_{n|n-1} + K_n\hat{\mathbf{e}}_n, \ \ \hat{\mathbf{x}}_n = \hat{\mathbf{x}}_{n|n} \\ P_{n|n} &= (I - K_nH)P_{n|n-1} \end{aligned}$$

end for

where $\hat{\mathbf{y}}_n \stackrel{\text{def}}{=} \hat{\mathbf{x}}_{n+1} - \Big(I - \big(D_{\mathbf{k}_r} + D_{\mathbf{k}}[(\mathbf{1}\mathbf{1}^T) \otimes I]\big)\Big)\hat{\mathbf{x}}_n$

$F_{11}(n) \stackrel{\text{def}}{=} \Big(\Delta G_k - \frac{1}{n_p}[H\mathbf{x}_n \otimes I]\Big)^t, \ \ F_{12}(\boldsymbol{\theta}) \stackrel{\text{def}}{=} \Big(I - A\Big(\boldsymbol{\theta}\Big)\Big)$

Though the parameters are static, if our initial estimate is bad the estimator might take a long time before converging. A commonly used technique to mitigate this is to allow the filter to explore the solution by adding small dynamic noise(time varying parameter). The variance of the dynamic noise is chosen heuristically. A large noise variance results in oscillations of the the estimate of the parameter while a very small noise variance would result in a very slow convergence of the estimator. Together with the time varying nature of the parameter, we can write a state space model as follows.

$$\begin{aligned} \hat{\boldsymbol{\theta}}_n &= F_{11}(n)\boldsymbol{\theta}_n + \mathbf{z}_n(\theta_{n-1}) \\ \boldsymbol{\theta}_n &= \boldsymbol{\theta}_{n-1} + \mathbf{z}_n^{\boldsymbol{\theta}} \end{aligned} \qquad (11)$$

where $E\Big[\mathbf{z}_n^{\boldsymbol{\theta}}\Big(\mathbf{z}_n^{\boldsymbol{\theta}}\Big)'\Big] = \sigma_{\boldsymbol{\theta}}^2 I_N \delta_{kl}$. The state space model in (11) is a linear model in $\boldsymbol{\theta}$. We employ a Kalman filtering based parameter estimation as summarized in Algorithm 2. The updated parameter estimate $\hat{\boldsymbol{\theta}}$ is fed back into Algorithm (1) and this iterative procedure can be repeated until convergence. The estimates of the states $\hat{\mathbf{x}}_n$ can be further improved

Algorithm 2 Kalman filtering: Parameter estimation

1. Initialization: $\hat{\boldsymbol{\theta}}_{0|0}, \ P_{0|0}^{\boldsymbol{\theta}}$
for n=1 to L **do**
2. Prediction:

$$\begin{aligned} \hat{\boldsymbol{\theta}}_{n|n-1} &= \hat{\boldsymbol{\theta}}_{n-|n-1}, \ \ P_{n|n-1}^{\boldsymbol{\theta}} = P_{n|n-1}^{\boldsymbol{\theta}} + \sigma_{\boldsymbol{\theta}}^2 I_N \\ \hat{\mathbf{e}}_n &= \hat{\mathbf{y}}_n - F_{11}(n)\hat{\boldsymbol{\theta}}_{n|n-1} \end{aligned}$$

2. Filtering:

$$K_n = P_{n|n-1}^{\boldsymbol{\theta}} F_{11}^T(n)\Big(F_{11}(n)P_{n|n-1}^{\boldsymbol{\theta}}F_{11}^T(n) + R_z(n,n)\big(\hat{\boldsymbol{\theta}}_{n|n-1}\big)\Big)$$

$$\hat{\boldsymbol{\theta}}_{n|n} = \hat{\boldsymbol{\theta}}_{n|n-1} + K_n\hat{\mathbf{e}}_n, \ \ P_{n|n}^{\boldsymbol{\theta}} = (I - K_nF_{11}(n))P_{n|n-1}^{\boldsymbol{\theta}}$$

end for
$\hat{\boldsymbol{\theta}} = \hat{\boldsymbol{\theta}}_{L|L}$

using a Kalman smoother. Algorithm (3) presents one of the most common fixed interval smoother, usually called the RTS (Rauch, Tung, and Striebel) smoother to obtain the smoothed estimates $\hat{\mathbf{x}}_n = \hat{\mathbf{x}}_{n|L}$. These estimates and inturn the parameter estimates obtained using the smoothed estimates are expected to be of higher quality compared to the filtered estimates.

Algorithm 3 Kalman smoothing: State estimation

Filtering steps from Algo. 2.

1. RTS smoother initialization: $\tilde{\mathbf{x}}_{L|L} = \hat{\mathbf{x}}_{L|L},\ \tilde{P}_{L|L} = \hat{P}_{L|L}$

for $n = L-1$ to 1 **do**

Smoothing:

$$K_s = P_{n|n}\Big(I - A\Delta\Big)^T P_{n+1|n}$$

$$\tilde{P}_{L|L} = P_{n|n} - K_s\Big(P_{n+1|n} - \tilde{P}_{L+1|L+1}\Big)K_s^T$$

$$\tilde{\mathbf{x}}_{n|L} = \hat{\mathbf{x}}_{n|n} + K_s\Big(\tilde{\mathbf{x}}_{n+1|L} - \mathbf{x}_{n+1|n}\Big),\ \ \hat{\mathbf{x}}_n = \hat{\mathbf{x}}_{n|L}$$

end for

V. Results

In this section, we present the simulation study to evaluate the performance of the proposed algorithm. We use normalized RMSE defined by $RMSE = \frac{1}{\sqrt{M}}E\left[\sqrt{\sum_{i=1}^{N}\left(\frac{n_i(0)-\hat{n}_i(0)}{n_i(0)}\right)^2}\right]$ as a metric for comparison. This would provide a common platform for comparing the performance for different realizations of the parameters and also different number of analytes.

In figure 1, we investigate the performance variation of the proposed algorithm with the observation noise variance. In the simulation set up, $M = N = 5, \Delta = 0.1, n_p = 10^7$ and the true parameters are randomly generated from $\mathcal{U}(0, 10^5)$. It can be seen that the performance degrades as the variance of the observation noise increases. The performance of the Kalman smoother based estimator outperforms the filter based scheme and also has relatively smaller performance degradation. The performance degradation of the smoother based scheme is negligible upto noise variance of 15dB.

Figure 2 shows the RMSE performance as a function of number of analytes. The performance degrades with the increase in number of analytes. The degradation is a consequence of estimating more number of parameters with the increase in the number of analytes. The performance of the smoother degrades less severely compared to the filter.

Figure 3 shows the RMSE performance improvement with the number of samples taken. Initially the performance improves significantly with the number of samples, but then the gains diminish with the increase in the number of samples. Again smoother based scheme outperforms the filter based scheme for smaller number of samples and for larger number of samples they behave identically.

VI. Conclusion

In this paper, we presented joint parameter-state estimation technique for inferring amounts of analytes present in a biological sample. The proposed method is based on a dual Kalman filter, and enables target quantification in the early phase of the binding reaction. Simulation results were provided to show the efficacy of the proposed algorithm.

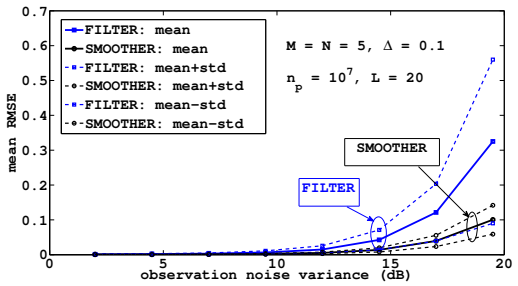

Fig. 1. *RMSE vs observation noise variance,* $M = N = 5, \Delta = 0.1, n_p = 10^7, L = 20$.

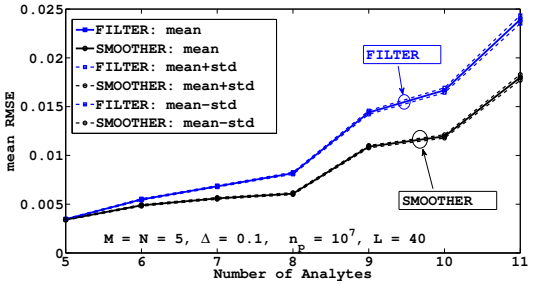

Fig. 2. *RMSE vs number of analytes,* $M = N = 5, \Delta = 0.1, n_p = 10^7, L = 40$.

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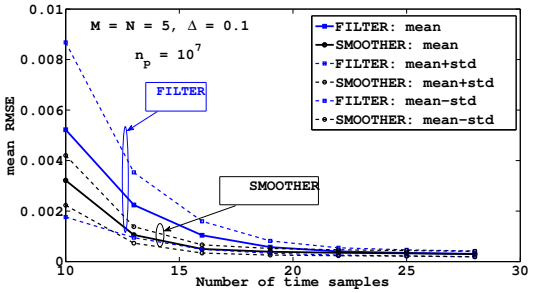

Fig. 3. *RMSE vs number of samples (L),* $M = N = 5, \Delta = 0.1, n_p = 10^7$.