

Channel Estimation Techniques for Diffusion-Based Molecular Communications

Vahid Jamali[†], Arman Ahmadzadeh[†], Christophe Jardin[‡], Heinrich Sticht[‡], and Robert Schober[†]

[†]Institute for Digital Communications, [‡]Institute for Biochemistry
Friedrich-Alexander University (FAU), Erlangen, Germany

Abstract—In molecular communication (MC) systems, the *expected* number of molecules observed at the receiver over time after the instantaneous release of molecules by the transmitter is referred to as the channel impulse response (CIR). Knowledge of the CIR is needed for the design of detection and equalization schemes. In this paper, we present a training-based CIR estimation framework for MC systems which aims at estimating the CIR based on the *observed* number of molecules at the receiver due to emission of a *sequence* of known numbers of molecules by the transmitter. In particular, we derive maximum likelihood (ML) and least sum of square errors (LSSE) estimators. We also study the Cramer Rao (CR) lower bound and training sequence design for the considered system. Simulation results confirm the analysis and compare the performance of the proposed estimation techniques with the CR lower bound.

I. INTRODUCTION

Recent advances in biology, nanotechnology, and medicine have enabled the possibility of communication in nano/micrometer scale environments [1]. Thereby, employing molecules as information carriers, molecular communication (MC) has quickly emerged as a bio-inspired approach for man-made communication systems in such environments. In fact, calcium signaling among neighboring cells, the use of neurotransmitters for communication across the synaptic cleft of neurons, and the exchange of autoinducers as signaling molecules in bacteria for quorum sensing are among the many examples of MC in nature [1].

A. Motivation

The design of any communication system crucially depends on the characteristics of the channel under consideration. In MC systems, the impact of the channel on the number of observed molecules can be captured by the channel impulse response (CIR) which is defined as the *expected* number of molecules counted at the receiver at time t after the instantaneous release of a known number of molecules by the transmitter at time $t = 0$. The CIR, denoted by $\bar{c}(t)$, can be used as the basis for the design of equalization and detection schemes for MC systems [2]–[4]. For diffusion-based MC, the released molecules move randomly according to Brownian motion which is caused by thermal vibration and collisions with other molecules in the fluid environment. Thereby, the average concentration of the molecules at a given coordinate $\mathbf{a} = [a_x, a_y, a_z]$ and at time t after release by the transmitter, denoted by $\bar{C}(\mathbf{a}, t)$, is governed by Fick's second

law of diffusion [3]. Finding $\bar{C}(\mathbf{a}, t)$ analytically involves solving partial differential equations and depends on initial and boundary conditions. Therefore, one possible approach for determining the CIR, which is widely employed in the literature [4], is to first derive a sufficiently accurate analytical expression for $\bar{C}(\mathbf{a}, t)$ for the considered MC channel from Fick's second law, and to subsequently integrate it over the receiver volume, V^{rec} , i.e.,

$$\bar{c}(t) = \iiint_{\mathbf{a} \in V^{\text{rec}}} \bar{C}(\mathbf{a}, t) da_x da_y da_z. \quad (1)$$

However, this approach may not be applicable in many practical scenarios as discussed in the following.

- The CIR can be obtained based on (1) only for the special case of a fully *transparent* receiver where it is assumed that the molecules move through the receiver as if it was not present in the environment. The assumption of a fully transparent receiver is a valid approximation only for some particular scenarios where the interaction of the receiver with the molecules can be neglected. However, for general receivers, the relationship between the concentration $\bar{C}(\mathbf{a}, t)$ and the number of observed molecules $\bar{c}(t)$ may not be as straightforward.
- Solving the differential equation associated with Fick's second law is possible only for simple and idealistic environments. For example, assuming a *point* source located at the origin of an *unbounded* environment and *impulsive* molecule release, $\bar{C}(\mathbf{a}, t)$ is obtained as [4]

$$\bar{C}(\mathbf{a}, t) = \frac{N^{\text{TX}}}{(4\pi Dt)^{3/2}} \exp\left(-\frac{|\mathbf{a}|^2}{4Dt}\right) \left[\frac{\text{molecules}}{\text{m}^3}\right], \quad (2)$$

where N^{TX} is the number of molecules released by the transmitter at $t = 0$ and D is the diffusion coefficient of the signaling molecule. However, $\bar{C}(\mathbf{a}, t)$ cannot be obtained in closed form for most practical MC environments which may involve difficult boundary conditions, non-instantaneous molecule release, flow, etc. Additionally, as has been shown in [5], the classical Fick's diffusion equation might even not be applicable in complex MC environments as physicochemical interactions with other objects in the channel, such as other molecules, cells, and microvessels, are not accounted for.

- Even if an expression for $\bar{C}(\mathbf{a}, t)$ can be obtained for a particular MC system, e.g. (2), it will be a function of several channel parameters such as the distance between the transmitter and the receiver and the diffusion coefficient. However, in practice, these parameters may not

be known a priori and also have to be estimated [6], [7]. This complicates finding the CIR based on $\bar{C}(\mathbf{a}, t)$.

Fortunately, for most communication problems, including equalization and detection, only the *expected* number of molecules that the receiver observed at the sampling times is needed [3], [4]. Therefore, knowledge of how the average concentration is related to the channel parameters is not required, and hence, the difficulties associated with deriving $\bar{C}(\mathbf{a}, t)$ can be avoided by directly estimating the CIR. Analytical expressions for the CIR for specific assumptions for the transmitter, channel, and receiver are available in the literature. For example, the CIR for an unbounded environment and a fully absorbing receiver is given in [8]. However, for general channel environments and receivers, a simple closed-form expression for the expected number of observed molecules $\bar{c}(t)$ may not exist. Even if such an expression can be derived, it is only valid for a particular MC environment and is still a function of several unknown parameters. Motivated by the above discussion, our goal in this paper is to develop a general CIR estimation framework for MC systems which is not limited to a particular MC channel model or a specific receiver type and does not require knowledge of the channel parameters.

B. Related Work

In most existing works on MC, the CIR is assumed to be perfectly known for receiver design [2]–[4], [9]. In the following, we review the relevant MC literature that focused on channel characterization. Estimation of the distance between a transmitter and a receiver was studied in [6], [7] for diffusive MC. In [10], an end-to-end mathematical model, including transmitter, channel, and receiver, was presented, and in [11], a stochastic channel model was proposed for flow-based and diffusion-based MC. For active transport MC, a Markov chain channel model was derived in [12]. Additionally, a unifying model including the effects of external noise sources and inter-symbol interference (ISI) was proposed for diffusive MC in [13]. In [14], the authors analyzed a microfluidic MC channel, propagation noise, and channel memory. However, the focus of [6], [7], [10]–[14] is either channel modeling or the estimation of channel parameters, i.e., the obtained results are not directly applicable to CIR acquisition.

In contrast to MC, for conventional wireless communication, there is a rich literature on channel estimation, mainly for linear channel models and impairment by additive white Gaussian noise (AWGN), see [15], [16], and the references therein. Channel estimation was also studied for non-linear and/or non-AWGN channels especially in optical communication. For example, for a photon-counting receiver, a linear time-invariant channel model with Poisson noise was considered in [17] and a non-linear channel model with Poisson noise was investigated in [18]. However, the MC channel model considered in this paper is neither linear nor impaired by AWGN and is also different from that in [18]. Therefore, the results known from conventional wireless communication are not directly applicable to MC.

C. Contributions

In contrast to [6]–[14], in this paper, we directly estimate the CIR based on the channel output, i.e., the number of molecules observed at the receiver. To the best of the authors' knowledge, this problem has not been studied in the MC literature, yet. In particular, we present a training-based CIR estimation framework which aims at estimating the CIR based on the detected number of molecules at the receiver due to the emission of a sequence of known numbers of molecules by the transmitter. To this end, we first derive the optimal maximum likelihood (ML) CIR estimator. Subsequently, we obtain the suboptimal least sum of square errors (LSSE) CIR estimator which entails a lower computational complexity than the ML estimator. Additionally, we derive the Cramer Rao (CR) bound which constitutes a lower bound on the estimation error variance of any unbiased estimator. We also study training sequence design for the considered MC system. Simulation results confirm the analysis and evaluate the performance of the proposed estimation techniques with respect to the CR lower bound.

Notations: We use the following notations throughout this paper: $\mathbb{E}_x\{\cdot\}$ denotes expectation with respect to random variable (RV) x and $[x]^+ = \max\{0, x\}$. Bold capital and small letters are used to denote matrices and vectors, respectively. $\mathbf{1}$ and $\mathbf{0}$ are vectors whose elements are all ones and zeros, respectively, \mathbf{A}^T denotes the transpose of \mathbf{A} , $\|\mathbf{a}\|$ represents the norm of vector \mathbf{a} , $[\mathbf{A}]_{mn}$ denotes the element in the m -th row and n -th column of matrix \mathbf{A} , $\text{tr}\{\mathbf{A}\}$ is the trace of matrix \mathbf{A} , $\text{diag}\{\mathbf{a}\}$ denotes a diagonal matrix with the elements of vector \mathbf{a} on its main diagonal, $\text{vdiag}\{\mathbf{A}\}$ is a vector which contains the diagonal entries of matrix \mathbf{A} , $\text{eig}\{\mathbf{A}\}$ is the set of eigen-values of matrix \mathbf{A} , $\mathbf{A} \succeq \mathbf{0}$ denotes a positive semidefinite matrix \mathbf{A} , and $\mathbf{a} \geq \mathbf{0}$ means that all the elements of vector \mathbf{a} are non-negative. Additionally, $\text{Pois}(\lambda)$ denotes a Poisson RV with mean λ , and $\text{Bin}(n, p)$ denotes a binomial RV for n trials and success probability p .

II. PROBLEM FORMULATION

In this section, we first present the considered MC channel model, and subsequently, formulate the CIR estimation problem.

A. System Model

We consider an MC system consisting of a transmitter, a channel, and a receiver. At the beginning of each symbol interval, the transmitter releases either N^{TX} or zero molecules, i.e., ON-OFF keying is performed. In this paper, we assume that the transmitter emits only one type of molecule. The released molecules propagate through the medium between the transmitter and the receiver. We assume that the movements of individual molecules are independent from each other. The receiver counts the number of observed molecules in each symbol interval. We note that this is a rather general model for the MC receiver which includes well-known receivers such as the transparent receiver [4] and the absorbing receiver [8].

Due to the memory of the MC channel, inter-symbol interference (ISI) occurs [13], [14]. In particular, ISI-free communication is only possible if the symbol intervals are

chosen sufficiently large such that the CIR fully decays to zero within one symbol interval which severely limits the transmission rate and results in an inefficient MC system design. Therefore, taking into account the effect of ISI, we assume the following input-output relation for the MC system

$$r[k] = \sum_{l=1}^L c_l[k] + c_n[k], \quad (3)$$

where $r[k]$ is the number of molecules detected at the receiver in symbol interval k , L is the number of memory taps of the channel, and $c_l[k]$ is the number of molecules observed at the receiver in symbol interval k due to the release of $s[k-l+1]N^{\text{Tx}}$ molecules by the transmitter in symbol interval $k-l+1$, where $s[k] \in \{0, 1\}$ holds. Thereby, $c_l[k]$ can be well approximated by a Poisson RV with mean $\bar{c}_l s[k-l+1]$, i.e., $c_l[k] \sim \text{Pois}(\bar{c}_l s[k-l+1])$, see [2], [3]. Moreover, $c_n[k]$ is the number of external noise molecules detected by the receiver in symbol interval k but not released by the transmitter. Noise molecules may originate from interfering sources which employ the same type of molecule as the considered MC system. Hence, $c_n[k]$ can also be modeled as a Poisson RV, i.e., $c_n[k] \sim \text{Pois}(\bar{c}_n)$, where $\bar{c}_n = \mathbb{E}\{c_n[k]\}$.

Remark 1: From a probabilistic point of view, we can assume that each molecule released by the transmitter in symbol interval $k-l+1$ is observed at the receiver in symbol interval k with a certain probability, denoted by p_l . Thereby, the probability that n molecules are observed at the receiver in symbol interval k due to the emission of N^{Tx} molecules in symbol interval $k-l+1$ follows a binomial distribution, i.e., $n \sim \text{Bin}(N^{\text{Tx}}, p_l)$. Moreover, assuming $N^{\text{Tx}} \rightarrow \infty$ while $N^{\text{Tx}} p_l \triangleq \bar{c}_l$ is fixed, the binomial distribution $\text{Bin}(N^{\text{Tx}}, p_l)$ converges to the Poisson distribution $\text{Pois}(\bar{c}_l)$ [19]. This is a valid assumption in MC since the number of released molecules is often very large to ensure that a sufficient number of molecules reaches the receiver. The same reasoning applies to the noise molecules.

Unlike the conventional linear input-output model for channels with memory in wireless communication systems [15], [16], the channel model in (3) is not linear since $s[k-l+1]$ does not affect the observation $r[k]$ directly but via Poisson RV $c_l[k]$. However, the *expectation* of the received signal is linearly dependent on the transmitted signal, i.e.,

$$\bar{r}[k] = \mathbb{E}\{r[k]\} = \sum_{l=1}^L \bar{c}_l s[k-l+1] + \bar{c}_n. \quad (4)$$

We note that for a given $s[k]$, in general, the actual number of molecules observed at the receiver, $r[k]$, will differ from the expected number of observed molecules, $\bar{r}[k]$, due to the intrinsic noisiness of diffusion.

B. CIR Estimation Problem

Let $\mathbf{s} = [s[1], s[2], \dots, s[K]]^T$ be a training sequence of length K . Here, we assume continuous transmission. Therefore, in order to ensure that the received signal is only affected by the training sequence \mathbf{s} and not by the transmissions in previous symbol intervals, we only employ $r[k]$, $k \geq L$, for CIR estimation. Thereby, the $K-L+1$ samples used for CIR

estimation are given by

$$r[L] = \text{Pois}(\bar{c}_1 s[L]) + \text{Pois}(\bar{c}_2 s[L-1]) + \dots + \text{Pois}(\bar{c}_L s[1]) + \text{Pois}(\bar{c}_n) \quad (5a)$$

$$r[L+1] = \text{Pois}(\bar{c}_1 s[L+1]) + \text{Pois}(\bar{c}_2 s[L]) + \dots + \text{Pois}(\bar{c}_L s[2]) + \text{Pois}(\bar{c}_n) \quad (5b)$$

\vdots

$$r[K] = \text{Pois}(\bar{c}_1 s[K]) + \text{Pois}(\bar{c}_2 s[K-1]) + \dots + \text{Pois}(\bar{c}_L s[K-L+1]) + \text{Pois}(\bar{c}_n). \quad (5c)$$

For convenience of notation, we define $\mathbf{r} = [r[L], r[L+1], \dots, r[K]]^T$ and $\bar{\mathbf{c}} = [\bar{c}_1, \bar{c}_2, \dots, \bar{c}_L, \bar{c}_n]^T$, and $f_{\mathbf{r}}(\mathbf{r}|\bar{\mathbf{c}}, \mathbf{s})$ is the probability density distribution (PDF) of observation \mathbf{r} conditioned on a given channel $\bar{\mathbf{c}}$ and a given training sequence \mathbf{s} . We assume that the CIR¹, $\bar{\mathbf{c}}$, remains unchanged for a sufficiently large block of symbol intervals during which CIR estimation and data transmission are performed. However, the CIR may change from one block to the next due to e.g. a change in the distance between transmitter and receiver. To summarize, in each block, the stochastic model in (3) is characterized by $\bar{\mathbf{c}}$ and our goal in this paper is to estimate $\bar{\mathbf{c}}$ based on the vector of random observations \mathbf{r} .

III. CIR ESTIMATION

In this section, we derive the ML and LSSE estimators as well as the CR lower bound for CIR estimation in MC.

A. ML CIR Estimation

The ML CIR estimator chooses the CIR which maximizes the likelihood of observation vector \mathbf{r} [19]. In particular, the ML estimator is given by

$$\hat{\bar{\mathbf{c}}}^{\text{ML}} = \underset{\bar{\mathbf{c}} \geq \mathbf{0}}{\text{argmax}} f_{\mathbf{r}}(\mathbf{r}|\bar{\mathbf{c}}, \mathbf{s}). \quad (6)$$

We assume that the observations in different symbol intervals are independent, i.e., $r[k]$ is independent of $r[k']$ for $k \neq k'$. This assumption is valid in practice if the time interval between two consecutive samples is sufficiently large, see [3] for a detailed discussion. Moreover, from (3), we observe that $r[k]$ is a sum of Poisson RVs. Hence, $r[k]$ is also a Poisson RV with its mean equal to the sum of the means of the summands, i.e., $r[k] \sim \text{Pois}(\bar{r}[k])$ with $\bar{r}[k] = \bar{c}_n + \sum_{l=1}^L \bar{c}_l s[k-l+1] = \bar{\mathbf{c}}^T \mathbf{s}_k$ and $\mathbf{s}_k = [s[k], s[k-1], \dots, s[k-L+1], 1]^T$. Therefore, $f_{\mathbf{r}}(\mathbf{r}|\bar{\mathbf{c}}, \mathbf{s})$ is given by

$$f_{\mathbf{r}}(\mathbf{r}|\bar{\mathbf{c}}, \mathbf{s}) = \prod_{k=L}^K \frac{(\bar{\mathbf{c}}^T \mathbf{s}_k)^{r[k]} \exp(-\bar{\mathbf{c}}^T \mathbf{s}_k)}{r[k]!}. \quad (7)$$

Maximizing $f_{\mathbf{r}}(\mathbf{r}|\bar{\mathbf{c}}, \mathbf{s})$ is equivalent to maximizing $\ln(f_{\mathbf{r}}(\mathbf{r}|\bar{\mathbf{c}}, \mathbf{s}))$ since $\ln(\cdot)$ is a monotonically increasing function. Hence, the ML estimate can be rewritten as

$$\hat{\bar{\mathbf{c}}}^{\text{ML}} = \underset{\bar{\mathbf{c}} \geq \mathbf{0}}{\text{argmax}} g(\bar{\mathbf{c}}) \quad \text{where} \quad (8)$$

$$g(\bar{\mathbf{c}}) \triangleq \sum_{k=L}^K \left[-\bar{\mathbf{c}}^T \mathbf{s}_k + r[k] \ln(\bar{\mathbf{c}}^T \mathbf{s}_k) \right].$$

¹With a slight abuse of notation, in the following, we refer to vector $\bar{\mathbf{c}}$ as the CIR although $\bar{\mathbf{c}}$ also contains the mean of the noise \bar{c}_n .

To present the solution of the above optimization problem rigorously, we first define some auxiliary variables. Let $\mathcal{A} = \{\mathcal{A}_1, \mathcal{A}_2, \dots, \mathcal{A}_N\}$ denote a set which contains all possible $N = 2^{L+1} - 1$ subsets of set $\mathcal{F} = \{1, 2, \dots, L, n\}$ except the empty set. Here, \mathcal{A}_n , $n = 1, 2, \dots, N$, denotes the n -th subset of \mathcal{A} . Moreover, let $\bar{c}^{\mathcal{A}_n}$ and $\mathbf{s}_k^{\mathcal{A}_n}$ denote reduced-dimension versions of \bar{c} and \mathbf{s}_k , respectively, which contain only the elements of \bar{c} and \mathbf{s}_k whose indices are in set \mathcal{A}_n , respectively.

Lemma 1: The ML estimator of the CIR for the considered MC channel is given by Algorithm 1 where the following nonlinear system of equations is solved² for different \mathcal{A}_n

$$\sum_{k=L}^K \left[\frac{r[k]}{(\bar{c}^{\mathcal{A}_n})^T \mathbf{s}_k^{\mathcal{A}_n}} - 1 \right] \mathbf{s}_k^{\mathcal{A}_n} = \mathbf{0}. \quad (9)$$

Proof: The problem in (8) is a convex optimization problem in variable \bar{c} because $g(\bar{c})$ is a concave function in \bar{c} and the feasible set $\bar{c} \geq \mathbf{0}$ is linear in \bar{c} . In particular, $\ln(\bar{c}^T \mathbf{s}_k)$ is concave since $\bar{c}^T \mathbf{s}_k$ is affine and the log-function is concave [20, Chapter 3]. Therefore, $g(\bar{c})$ is a sum of weighted concave terms $r[k] \ln(\bar{c}^T \mathbf{s}_k)$ and affine terms $\bar{c}^T \mathbf{s}_k$ which in turn yields a concave function [20, Chapter 3]. For the constrained convex problem in (8), the optimal solution falls into one of the following two categories:

Stationary Point: In this case, the optimal solution is found by taking the derivative of $g(\bar{c})$ with respect to \bar{c} and setting $\bar{c}^{\mathcal{F}} = \bar{c}$ and $\mathbf{s}_k^{\mathcal{F}} = \mathbf{s}_k$ which leads to (9) for $\mathcal{A}_n = \mathcal{F}$. Note that this stationary point is the global optimal solution of the unconstrained version of the problem in (8), i.e., when constraint $\bar{c} \geq \mathbf{0}$ is dropped. Therefore, if $\bar{c}^{\mathcal{F}}$ is in the feasible set, i.e., $\bar{c}^{\mathcal{F}} \geq \mathbf{0}$ holds, it is also the optimal solution of the constrained problem in (8) and hence, we obtain $\hat{c}^{\text{ML}} = \bar{c}^{\mathcal{F}}$.

Boundary Point: In this case, for the optimal solution, some of the elements of \bar{c} are zero. Since it is not a priori known which elements are zero, we have to consider all possible cases. To do so, we use auxiliary variables $\bar{c}^{\mathcal{A}_n}$ and $\mathbf{s}_k^{\mathcal{A}_n}$ where set \mathcal{A}_n specifies the indices of the non-zero elements of \bar{c} . For a given \mathcal{A}_n , we formulate a new problem by substituting $\bar{c}^{\mathcal{A}_n}$ and $\mathbf{s}_k^{\mathcal{A}_n}$ for \bar{c} and \mathbf{s}_k in (8), respectively. The solution of the *new problem* is now a stationary point not a boundary point since a boundary point implies that some of the elements of $\bar{c}^{\mathcal{A}_n}$ are zero which yields a contradiction because we assumed that $\bar{c}^{\mathcal{A}_n}$ includes the non-zero elements of \bar{c} . The stationary point of the new problem can be found by taking the derivative of $g(\bar{c}^{\mathcal{A}_n})$ with respect to $\bar{c}^{\mathcal{A}_n}$ which leads to (9). Here, if $\bar{c}^{\mathcal{A}_n} \geq \mathbf{0}$ does not hold, we discard $\bar{c}^{\mathcal{A}_n}$, otherwise, it is a candidate for the optimal solution. Therefore, we construct the candidate ML CIR estimate, denoted by \hat{c}^{CAN} , such that the elements of \hat{c}^{CAN} whose indices are in \mathcal{A}_n are equal to the values of the corresponding elements in $\bar{c}^{\mathcal{A}_n}$ and the remaining elements are equal to zero. The resulting \hat{c}^{CAN} is saved in the candidate set \mathcal{C} . Finally, the ML estimate, \hat{c}^{ML} , is given by that \hat{c}^{CAN} in set \mathcal{C} which maximizes $g(\bar{c})$.

The above results are concisely summarized in Algorithm 1 which concludes the proof. ■

Remark 2: Let us assume a priori that all L taps and the

²The system of nonlinear equations in (9) can be solved using standard mathematical software packages such as Mathematica.

Algorithm 1 ML/LSSE CIR Estimate $\hat{c}^{\text{ML}}/\hat{c}^{\text{LSSE}}$

```

initialize  $\mathcal{A}_n = \mathcal{F}$  and solve (9)/(12) to find  $\bar{c}^{\mathcal{F}}$ 
if  $\bar{c}^{\mathcal{F}} \geq \mathbf{0}$  then
  Set  $\hat{c}^{\text{ML}} = \bar{c}^{\mathcal{F}}/\hat{c}^{\text{LSSE}} = \bar{c}^{\mathcal{F}}$ 
else
  for  $\forall \mathcal{A}_n \neq \mathcal{F}$  do
    Solve (9)/(12) to find  $\bar{c}^{\mathcal{A}_n}$ 
    if  $\bar{c}^{\mathcal{A}_n} \geq \mathbf{0}$  holds then
      Set the values of the elements of  $\hat{c}^{\text{CAN}}$ , whose indices
      are in  $\mathcal{A}_n$ , equal to the values of the corresponding
      elements in  $\bar{c}^{\mathcal{A}_n}$  and the remaining elements equal
      to zero;
      Save  $\hat{c}^{\text{CAN}}$  in the candidate set  $\mathcal{C}$ 
    else
      Discard  $\bar{c}^{\mathcal{A}_n}$ 
    end if
  end for
  Choose  $\hat{c}^{\text{ML}}/\hat{c}^{\text{LSSE}}$  equal to that  $\hat{c}^{\text{CAN}}$  in the candidate set
   $\mathcal{C}$  which maximizes  $g(\bar{c})$ /minimizes  $\|\epsilon\|^2$ 
end if

```

noise mean are non-zero, i.e., $\bar{c} > \mathbf{0}$. Thereby, the consistency property of ML estimation [19, Chapter 4] implies that under some regularity conditions, notably that the likelihood is a continuous function of \bar{c} and that \bar{c} is not on the boundary of the parameter set $\bar{c} \geq \mathbf{0}$, we obtain $\mathbb{E}\{\hat{c}^{\text{ML}}\} \rightarrow \bar{c}$ as $K \rightarrow \infty$. In other words, the ML estimator is asymptotically unbiased. Therefore, for large values of K , the ML estimator becomes sufficiently accurate such that none of the elements of \hat{c}^{ML} is zero. In this case, Algorithm 1 reduces to directly solving (9) for $\mathcal{A}_n = \mathcal{F}$.

B. LSSE CIR Estimation

The LSSE CIR estimator chooses that \bar{c} which minimizes the sum of the square errors for the observation vector \mathbf{r} . Thereby, the error vector is defined as $\epsilon = \mathbf{r} - \mathbb{E}\{\mathbf{r}\} = \mathbf{r} - \mathbf{S}\bar{c}$ where $\mathbf{S} = [\mathbf{s}_L, \mathbf{s}_{L+1}, \dots, \mathbf{s}_K]^T$. In particular, the LSSE CIR estimate can be written as

$$\hat{c}^{\text{LSSE}} = \underset{\bar{c} \geq \mathbf{0}}{\text{argmin}} \|\epsilon\|^2 = \|\mathbf{r} - \mathbf{S}\bar{c}\|^2. \quad (10)$$

The square of the norm of the error vector is obtained as

$$\begin{aligned} \|\epsilon\|^2 &= \text{tr}\{\epsilon\epsilon^T\} = \text{tr}\{(\mathbf{r} - \mathbf{S}\bar{c})(\mathbf{r} - \mathbf{S}\bar{c})^T\} \\ &= \text{tr}\{\mathbf{S}^T \mathbf{S} \bar{c} \bar{c}^T\} - 2\text{tr}\{\mathbf{r}^T \mathbf{S} \bar{c}\} + \text{tr}\{\mathbf{r} \mathbf{r}^T\}, \end{aligned} \quad (11)$$

where we used the following properties of the trace: $\text{tr}\{\mathbf{A}\} = \text{tr}\{\mathbf{A}^T\}$ and $\text{tr}\{\mathbf{A}\mathbf{B}\} = \text{tr}\{\mathbf{B}\mathbf{A}\}$ [21]. The LSSE estimate is given in the following lemma where we use the auxiliary matrix $\mathbf{S}^{\mathcal{A}_n} = [\mathbf{s}_L^{\mathcal{A}_n}, \mathbf{s}_{L+1}^{\mathcal{A}_n}, \dots, \mathbf{s}_K^{\mathcal{A}_n}]^T$.

Lemma 2: The LSSE estimator of the CIR for the considered MC channel is given by Algorithm 1 where for a given set \mathcal{A}_n , $\bar{c}^{\mathcal{A}_n}$ is obtained as

$$\bar{c}^{\mathcal{A}_n} = ((\mathbf{S}^{\mathcal{A}_n})^T \mathbf{S}^{\mathcal{A}_n})^{-1} (\mathbf{S}^{\mathcal{A}_n})^T \mathbf{r}. \quad (12)$$

Proof: The optimization problem in (10) is convex since $\|\epsilon\|^2$ is quadratic in variable \bar{c} , $\mathbf{S}^T \mathbf{S} \succeq \mathbf{0}$ holds, and the feasibility set $\bar{c} \geq \mathbf{0}$ is linear in \bar{c} [20, Chapter 4]. Hence, the constrained convex problem in (10) can be solved using a similar methodology as was used to find the ML estimate in Lemma 1. This leads to Lemma 2. ■

Remark 3: The LSSE estimator employs in fact a linear filter to compute $\bar{\mathbf{c}}^{A_n}$, i.e., $\bar{\mathbf{c}}^{A_n} = \mathbf{F}^{A_n} \mathbf{r}$ where $\mathbf{F}^{A_n} = ((\mathbf{S}^{A_n})^T \mathbf{S}^{A_n})^{-1} (\mathbf{S}^{A_n})^T$. Moreover, since the training sequence \mathbf{s} is fixed, matrix \mathbf{F}^{A_n} can be calculated offline and then be used for online CIR estimation. Therefore, the calculation of $\hat{\mathbf{c}}^{A_n}$ for the LSSE estimator in (12) is considerably less computationally complex than the computation of $\hat{\mathbf{c}}^{A_n}$ for the ML estimator in (9) which requires solving a system of nonlinear equations.

C. CR Lower Bound

The CR bound is a lower bound on the variance of any unbiased estimator of a deterministic parameter [19]. In particular, under some regularity conditions, the covariance matrix of any unbiased estimate of parameter $\bar{\mathbf{c}}$, denoted by $\mathbf{C}(\hat{\bar{\mathbf{c}}})$, satisfies

$$\mathbf{C}(\hat{\bar{\mathbf{c}}}) - \mathbf{I}^{-1}(\bar{\mathbf{c}}) \succeq \mathbf{0}, \quad (13)$$

where $\mathbf{I}(\bar{\mathbf{c}})$ is the Fisher information matrix of parameter vector $\bar{\mathbf{c}}$ where the elements of $\mathbf{I}(\bar{\mathbf{c}})$ are given by

$$[\mathbf{I}(\bar{\mathbf{c}})]_{i,j} = -\mathbb{E}_{\mathbf{r}|\bar{\mathbf{c}}} \left\{ \frac{\partial^2 \ln \{f_{\mathbf{r}}(\mathbf{r}|\bar{\mathbf{c}}, \mathbf{s})\}}{\partial \bar{\mathbf{c}}[i] \partial \bar{\mathbf{c}}[j]} \right\}. \quad (14)$$

We note that for a positive semidefinite matrix, the diagonal elements are non-negative, i.e., $[\mathbf{C}(\hat{\bar{\mathbf{c}}}) - \mathbf{I}^{-1}(\bar{\mathbf{c}})]_{i,i} \geq 0$. Therefore, for an unbiased estimator, i.e., $\mathbb{E}\{\hat{\bar{\mathbf{c}}}\} = \bar{\mathbf{c}}$ holds, with the estimation error vector defined as $\mathbf{e} = \bar{\mathbf{c}} - \hat{\bar{\mathbf{c}}}$, the CR bound provides the following lower bound on the sum of the expected square errors

$$\mathbb{E}_{\mathbf{r}|\bar{\mathbf{c}}} \{\|\mathbf{e}\|^2\} \geq \text{tr} \{ \mathbf{I}^{-1}(\bar{\mathbf{c}}) \} = \text{tr} \left\{ \left[\sum_{k=L}^K \frac{\mathbf{s}_k \mathbf{s}_k^T}{\bar{\mathbf{c}}^T \mathbf{s}_k} \right]^{-1} \right\}. \quad (15)$$

Remark 4: We note that the ML and LSSE estimators in Algorithm 1 are biased in general. Hence, the error variances of the ML and LSSE estimates may fall below the CR bound. However, as $K \rightarrow \infty$, the ML and LSSE estimators become asymptotically unbiased, cf. Remark 2, and the CR bound becomes a valid lower bound. The asymptotic unbiasedness of the proposed estimators is also numerically verified in Section V, cf. Fig. 1.

IV. TRAINING SEQUENCE DESIGN

In the following, we present two different training sequence designs for CIR estimation in MC systems.

A. LSSE-Based Training Sequence Design

We first consider a training sequence design which minimizes an *upper bound* on the *average* estimation error for the LSSE estimator. First, we note that for training sequence design, the estimation error has to be averaged over both \mathbf{r} and $\bar{\mathbf{c}}$ since both are unknown, and hence, have to be modeled as RVs. Again, we assume a priori that all L taps and the noise mean are non-zero. Therefore, neglecting the information that $\bar{\mathbf{c}} \geq \mathbf{0}$ has to hold in (10) yields an upper bound on the estimation error for the LSSE estimator. This upper bound is adopted here for the problem of sequence design since the solution of (10) after dropping constraint $\bar{\mathbf{c}} \geq \mathbf{0}$ lends itself to an elegant closed-form solution for the estimated CIR given

by $\hat{\bar{\mathbf{c}}}_{\text{up}}^{\text{LSSE}} = (\mathbf{S}^T \mathbf{S})^{-1} \mathbf{S}^T \mathbf{r}$, which can be used as the basis for either a computer-based search or even a systematic approach to find good training sequences. Moreover, this upper bound is tight as $K \rightarrow \infty$ since $\hat{\bar{\mathbf{c}}}_{\text{up}}^{\text{LSSE}} > \mathbf{0}$ holds and we obtain $\hat{\bar{\mathbf{c}}}_{\text{up}}^{\text{LSSE}} = \hat{\bar{\mathbf{c}}}_{\text{up}}^{\text{LSSE}}$. In Fig. 3, we show numerically that even for short sequence lengths, this upper bound is not loose.

Defining the estimation error as $\mathbf{e}_{\text{up}}^{\text{LSSE}} = \bar{\mathbf{c}} - \hat{\bar{\mathbf{c}}}_{\text{up}}^{\text{LSSE}}$, the expected square error norm is obtained as

$$\begin{aligned} & \mathbb{E}_{\mathbf{r}, \bar{\mathbf{c}}} \{ \|\mathbf{e}_{\text{up}}^{\text{LSSE}}\|^2 \} \\ &= \mathbb{E}_{\mathbf{r}, \bar{\mathbf{c}}} \left\{ \text{tr} \left\{ \left(\bar{\mathbf{c}} - (\mathbf{S}^T \mathbf{S})^{-1} \mathbf{S}^T \mathbf{r} \right) \left(\bar{\mathbf{c}} - (\mathbf{S}^T \mathbf{S})^{-1} \mathbf{S}^T \mathbf{r} \right)^T \right\} \right\} \\ &= \mathbb{E}_{\mathbf{r}, \bar{\mathbf{c}}} \left\{ \text{tr} \left\{ (\mathbf{S}^T \mathbf{S})^{-1} \mathbf{S}^T \mathbf{r} \mathbf{r}^T \mathbf{S} (\mathbf{S}^T \mathbf{S})^{-1} \right\} \right. \\ & \quad \left. - 2 \text{tr} \left\{ \bar{\mathbf{c}}^T \mathbf{S} (\mathbf{S}^T \mathbf{S})^{-1} \right\} + \text{tr} \{ \bar{\mathbf{c}} \bar{\mathbf{c}}^T \} \right\}. \end{aligned} \quad (16)$$

Next, we calculate the expectation over $(\mathbf{r}, \bar{\mathbf{c}})$ in (16) in two steps, first with respect to \mathbf{r} conditioned on $\bar{\mathbf{c}}$ and then with respect to $\bar{\mathbf{c}}$. To this end, we use $\mathbb{E}_{\mathbf{X}} \{ \text{tr} \{ \mathbf{A} \mathbf{X} \mathbf{B} \} \} = \text{tr} \{ \mathbf{A} \mathbb{E}_{\mathbf{X}} \{ \mathbf{X} \} \mathbf{B} \}$, which is valid for general matrices \mathbf{A} , \mathbf{B} , and \mathbf{X} , and $\mathbb{E}_{\mathbf{x}} \{ \mathbf{x} \mathbf{x}^T \} = \boldsymbol{\lambda} \boldsymbol{\lambda}^T + \text{diag} \{ \boldsymbol{\lambda} \}$, which is valid for multivariate Poisson random vectors \mathbf{x} with covariance matrix $\mathbf{C}(\mathbf{x}) = \text{diag} \{ \boldsymbol{\lambda} \}$. Hence, $\mathbb{E} \{ \|\mathbf{e}_{\text{up}}^{\text{LSSE}}\|^2 \}$ can be calculated as

$$\begin{aligned} & \mathbb{E}_{\bar{\mathbf{c}}} \mathbb{E}_{\mathbf{r}|\bar{\mathbf{c}}} \{ \|\mathbf{e}_{\text{up}}^{\text{LSSE}}\|^2 \} \\ &= \mathbb{E}_{\bar{\mathbf{c}}} \left\{ \text{tr} \left\{ (\mathbf{S}^T \mathbf{S})^{-1} \mathbf{S}^T (\mathbf{S} \bar{\mathbf{c}} \bar{\mathbf{c}}^T \mathbf{S}^T) \mathbf{S} (\mathbf{S}^T \mathbf{S})^{-1} \right\} \right. \\ & \quad \left. - 2 \text{tr} \left\{ \bar{\mathbf{c}} \bar{\mathbf{c}}^T \mathbf{S}^T \mathbf{S} (\mathbf{S}^T \mathbf{S})^{-1} \right\} + \text{tr} \{ \bar{\mathbf{c}} \bar{\mathbf{c}}^T \} \right. \\ & \quad \left. + \text{tr} \left\{ (\mathbf{S}^T \mathbf{S})^{-1} \mathbf{S}^T \text{diag} \{ \mathbf{S} \bar{\mathbf{c}} \} \mathbf{S} (\mathbf{S}^T \mathbf{S})^{-1} \right\} \right\} \\ &= \mathbb{E}_{\bar{\mathbf{c}}} \left\{ \text{tr} \left\{ \mathbf{S} (\mathbf{S}^T \mathbf{S})^{-2} \mathbf{S}^T \text{diag} \{ \mathbf{S} \bar{\mathbf{c}} \} \right\} \right\} \\ &= \text{tr} \left\{ \mathbf{S}^T \text{vdiag} \left\{ \mathbf{S} (\mathbf{S}^T \mathbf{S})^{-2} \mathbf{S}^T \right\} \boldsymbol{\mu}_{\bar{\mathbf{c}}}^T \right\}, \end{aligned} \quad (17)$$

where $\boldsymbol{\mu}_{\bar{\mathbf{c}}} = \mathbb{E}_{\bar{\mathbf{c}}} \{ \bar{\mathbf{c}} \}$.

Remark 5: The evaluation of the expression in (17) can be numerically challenging due to the required inversion of matrix $\mathbf{S}^T \mathbf{S}$, especially when one of the eigen-values of $\mathbf{S}^T \mathbf{S}$ is close to zero. One way to cope with this problem is to eliminate all sequences resulting in close-to-zero eigen-values for matrix $\mathbf{S}^T \mathbf{S}$ during the search. Formally, we can adopt the following search criterion for training sequence design

$$\mathbf{s}^* = \underset{\mathbf{s} \in \mathcal{S}}{\text{argmin}} \text{tr} \left\{ \mathbf{S}^T \text{vdiag} \left\{ \mathbf{S} (\mathbf{S}^T \mathbf{S})^{-2} \mathbf{S}^T \right\} \boldsymbol{\mu}_{\bar{\mathbf{c}}}^T \right\}, \quad (18)$$

where $\mathcal{S} = \{ \mathbf{s} \mid |x| > \varepsilon, \forall x \in \text{eig} \{ \mathbf{S}^T \mathbf{S} \} \}$ and ε is a small number which guarantees that the eigen-values of matrix $\mathbf{S}^T \mathbf{S}$ are not close to zero, e.g., in Section V, we choose $\varepsilon = 10^{-9}$.

B. ISI-Free Training Sequence Design

One simple approach to estimate the CIR is to construct a training sequence such that ISI is avoided during estimation. In this case, in each symbol interval, the receiver will observe molecules which have been released by the transmitter in only one symbol interval and not in multiple symbol intervals. To this end, the transmitter releases N^{Tx} molecules every $L + 1$ symbol intervals and remains silent for the rest of the

symbol intervals. In particular, the sequence \mathbf{s} is constructed as follows:

$$s[k] = \begin{cases} 1, & \text{if } \frac{k-k_0}{L+1} \in \mathbb{Z} \\ 0, & \text{otherwise} \end{cases} \quad (19)$$

where $k \in \{1, \dots, K\}$, and k_0 is the index of the first symbol interval in which the transmitter releases molecules. Moreover, for this training sequence, the CIR can be straightforwardly estimated as

$$\hat{c}_l^{\text{ISIF}} = \frac{1}{|\mathcal{K}_l|} \left[\sum_{k \in \mathcal{K}_l} [r[k] - \hat{c}_n^{\text{ISIF}}] \right]^+, \quad l = 1, \dots, L \quad (20a)$$

$$\hat{c}_n^{\text{ISIF}} = \frac{1}{|\mathcal{K}_n|} \sum_{k \in \mathcal{K}_n} r[k], \quad (20b)$$

where $\mathcal{K}_l = \{k | \frac{k-k_0-l+1}{L+1} \in \mathbb{Z} \wedge k \in \{1, \dots, K\}\}$, $\mathcal{K}_n = \{k | \frac{k-k_0-L}{L+1} \in \mathbb{Z} \wedge k \in \{1, \dots, K\}\}$, and $[\cdot]^+$ is needed to ensure that all estimated channel taps are non-negative, i.e., $\hat{\mathbf{c}}^{\text{ISIF}} \geq \mathbf{0}$ holds.

V. PERFORMANCE EVALUATION

In this section, we evaluate the performances of the different estimation techniques and training sequence designs developed in this paper. For simplicity, for the results provided in this section, we generate the CIR $\bar{\mathbf{c}}$ based on (1) and (2). However, we emphasize that the proposed estimation framework is not limited to the particular channel and receiver models assumed in (1) and (2). We use (1) and (2) only to obtain a $\bar{\mathbf{c}}$ which is representative of a typical CIR in MC. In particular, we assume a point source with impulsive molecule release and $N^{\text{Tx}} = 10^5$, a fully transparent spherical receiver with radius 45 nm, and an unbounded environment with $D = 4.365 \times 10^{-10} \frac{\text{m}^2}{\text{s}}$ [9]. Additionally, we assume that the distance between the transmitter and the receiver is given by $|\mathbf{a}| = |\bar{\mathbf{a}}| + \tilde{a}$ nm where $|\bar{\mathbf{a}}| = 500$ nm and \tilde{a} is a RV uniformly distributed in the interval $[-\hat{a}, \hat{a}]$. The receiver counts the number of molecules once per symbol interval at time $T_{\text{smp}} = \arg\max_t \bar{\mathcal{C}}(\bar{\mathbf{a}}, t)$ after the beginning of the symbol interval where $\bar{\mathcal{C}}(\bar{\mathbf{a}}, t)$ is computed based on (2). The noise mean is chosen as $\bar{c}_n = 0.5 \max_t \bar{\mathcal{C}}(\bar{\mathbf{a}}, t)$. Furthermore, the symbol duration and the number of taps L are chosen such that $\bar{c}_{L+1} < 0.1 \bar{c}_1$.

In order to compare the performances of the considered estimators quantitatively, we define the normalized mean and variance of the estimation error $\mathbf{e} = \hat{\mathbf{c}} - \bar{\mathbf{c}}$ as

$$\overline{\text{Mean}}_{\mathbf{e}} = \frac{\|\mathbb{E}\{\mathbf{e}\}\|^2}{\|\mathbb{E}\{\bar{\mathbf{c}}\}\|^2} \quad \text{and} \quad (21)$$

$$\overline{\text{Var}}_{\mathbf{e}} = \frac{\mathbb{E}\{\|\mathbf{e}\|^2\} - \|\mathbb{E}\{\mathbf{e}\}\|^2}{\|\mathbb{E}\{\bar{\mathbf{c}}\}\|^2}, \quad (22)$$

respectively. In Fig. 1, we show the normalized mean of the estimation error, $\overline{\text{Mean}}_{\mathbf{e}}$, in dB vs. the training sequence length, K , for $L \in \{1, 3, 5\}$. The training sequences are constructed by concatenating n copies of the binary sequence [1100100101] of length 10, i.e., $K = 10n$. Furthermore, for clarity of presentation, we assume $\hat{a} = 0$ which corresponds to a time-invariant environment with deterministic CIR. The results reported in Fig. 1 are Monte Carlo simulations where each point of the curves is obtained by averaging over 10^6

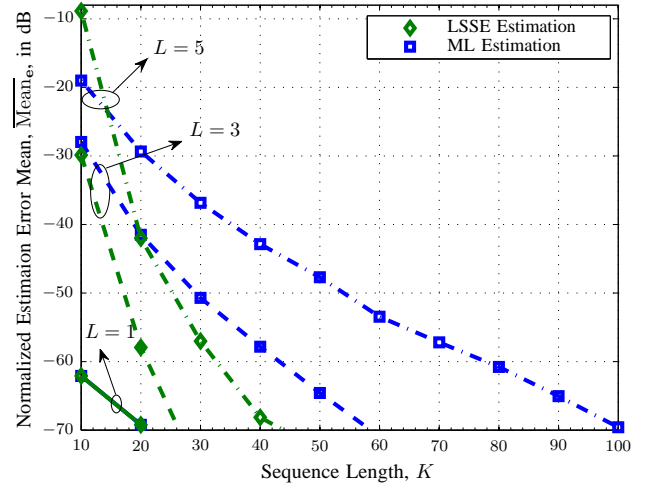


Fig. 1. Normalized estimation error mean, $\overline{\text{Mean}}_{\mathbf{e}}$, in dB vs. the training sequence length, K , for $L \in \{1, 3, 5\}$.

random realizations of observation vector \mathbf{r} . We observe that the normalized error mean decreases as the sequence length increases. Therefore, the ML and LSSE estimators are biased for short sequence lengths but as the sequence length increases, both the ML and LSSE estimators become asymptotically unbiased, i.e., $\mathbb{E}\{\hat{\mathbf{c}}\} \rightarrow \bar{\mathbf{c}}$ as $K \rightarrow \infty$. Furthermore, from Fig. 1, we observe that the error mean increases as the number of channel taps increases.

In Fig. 2, we show the normalized estimation error variance, $\overline{\text{Var}}_{\mathbf{e}}$, in dB vs. the training sequence length, K , for $L \in \{1, 3, 5\}$. The parameters used in Fig. 2 are identical to those used in Fig. 1. As expected, the variance of the estimation error decreases with increasing training sequence length. Moreover, for $L \in \{3, 5\}$, we observe that the variance of the estimation error for the LSSE estimator is slightly higher than that for the ML estimator, whereas for $L = 1$, the variance of the estimation error for the LSSE estimator coincides with that of the ML estimator. These results suggest that the simple LSSE estimator provides a favorable complexity-performance tradeoff for CIR estimation in the considered MC system. For short sequence lengths, the variances of the ML and LSSE estimators can even be lower than the CR bound as these estimators are biased and the CR bound is a valid lower bound only for unbiased estimators, see Fig. 1. However, as K increases, both the ML and LSSE estimators become asymptotically unbiased, see Fig. 1. Fig. 2 shows that, for large K , the error variance of the ML estimator coincides with the CR bound and the error variance of the LSSE estimator is very close to the CR bound. We note that for the adopted training sequence, the matrix inversion required in (15) cannot be computed for $K = 10$ and $L = 5$ since matrix $\sum_{k=L}^K \frac{\mathbf{s}_k \mathbf{s}_k^T}{\bar{\mathbf{c}}^T \mathbf{s}_k}$ has one zero eigen-value. Therefore, we do not report the value of the CR bound for this case in Fig. 2.

Next, we investigate the performances of the optimal and ISI-free training sequence designs developed in Section IV. Here, we employ a computer-based search to find the optimal sequence based on the criterion in (18) where $\varepsilon = 10^{-9}$. We consider short sequence lengths, i.e., $K \leq 20$, due to exponential increase of the computational complexity of the exhaustive search with respect to the sequence length. More-

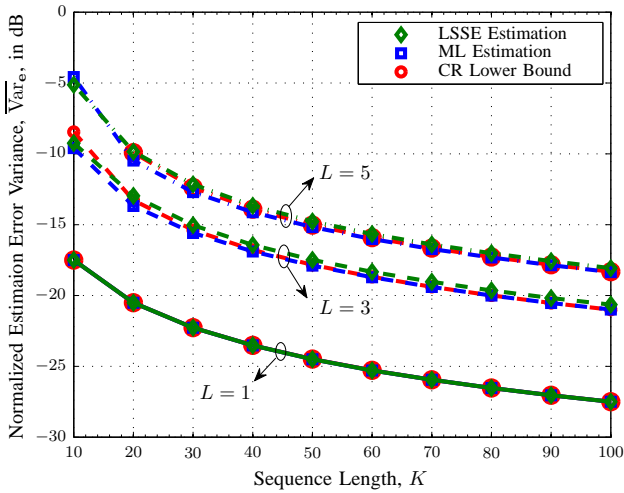


Fig. 2. Normalized estimation error variance, $\overline{\text{Var}}_e$, in dB vs. the training sequence length, K , for $L \in \{1, 3, 5\}$.

TABLE I

EXAMPLES OF OPTIMAL LSSE SEQUENCES OBTAINED BY A COMPUTER-BASED SEARCH FOR $L \in \{1, \dots, 5\}$ AND $K \in \{10, 16\}$.

	$K = 10$	$K = 16$
$L = 1$	$\mathbf{s}^* = [10101010]^T$	$\mathbf{s}^* = [01010101010101]^T$
$L = 2$	$\mathbf{s}^* = [0010001110]^T$	$\mathbf{s}^* = [0110011101000001]^T$
$L = 3$	$\mathbf{s}^* = [0100001101]^T$	$\mathbf{s}^* = [0101101101100000]^T$
$L = 4$	$\mathbf{s}^* = [1010110000]^T$	$\mathbf{s}^* = [1111100001000100]^T$
$L = 5$	$\mathbf{s}^* = [01110100010]^T$	$\mathbf{s}^* = [1001010011000000]^T$

over, since there are $L+1$ unknown parameters, we require at least $L+1$ observations for estimation, i.e., $K-L+1 \geq L+1$ or equivalently $K \geq 2L$. In Table I, we present the optimal sequences obtained for $L \in \{1, 2, 3, 4, 5\}$, $K \in \{10, 16\}$, and $\hat{a} = 100$ nm. We note that the optimal sequence which is obtained from (18) is not unique and only one of the optimal sequences is shown in Table I for each value of K and L . The optimal sequences shown in blue font in Table I are identical to the ISI-free sequences proposed in (19). In particular, for $L = 1$, the optimal sequences for both $K = 10$ and 16 are ISI-free, whereas for $L > 1$, none of the optimal sequences is ISI-free.

In Fig. 3, we show the normalized LSSE estimation error, $\overline{\text{Var}}_e$, in dB vs. the training sequence length, K , for $L \in \{1, 2, 3, 5\}$ and $\hat{a} = 100$ nm. Thereby, we report the analytical results for the upper bound in (17) and Monte Carlo simulation results for 10^6 random realizations. Fig. 3 confirms that (17) is a tight upper bound even for short sequence lengths. Moreover, we observe from Fig. 3 that the performance of the ISI-free sequence coincides with that of the optimal sequence for all sequence lengths when $L = 1$, and for $L > 1$, the difference between the error variances of the ISI-free sequence and the optimal sequence increases as L increases. This result suggests that for MC channels with small numbers of taps, a simple ISI-free training sequence is a suitable option. Furthermore, as expected, the estimation error decreases with increasing training sequence length.

VI. CONCLUSIONS

In this paper, we developed a training-based CIR estimation framework which enables the acquisition of the CIR based

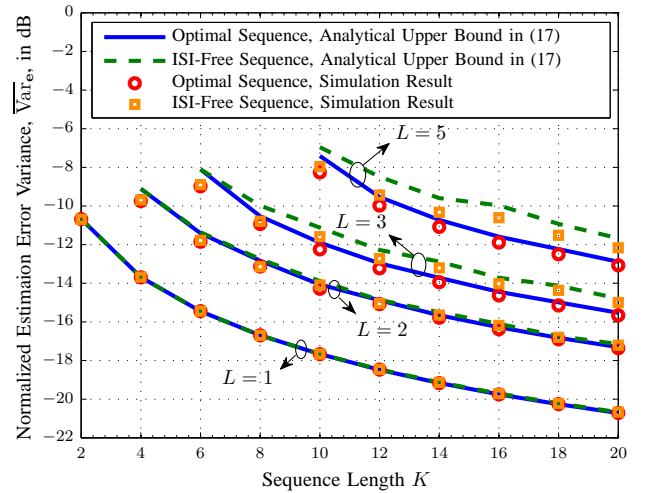


Fig. 3. Normalized LSSE estimation error variance, $\overline{\text{Var}}_e$, in dB vs. the training sequence length, K , for $L \in \{1, 2, 3, 5\}$.

on the observed number of molecules at the receiver due to emission of a sequence of known numbers of molecules by the transmitter. We derived the optimal ML estimator, the suboptimal LSSE estimator, and the CR lower bound. Furthermore, we studied both an optimal and a suboptimal training sequence design for the considered MC system. Simulation results confirmed the analysis and compared the performance of the proposed estimation techniques with the CR lower bound.

REFERENCES

- [1] T. Nakano, M. Moore, F. Wei, A. Vasilakos, and J. Shuai, "Molecular Communication and Networking: Opportunities and Challenges," *IEEE Trans. NanoBiosci.*, vol. 11, no. 2, pp. 135–148, June 2012.
- [2] H. Arjmandi, A. Gohari, M. Kenari, and F. Bateni, "Diffusion-Based Nanonetworking: A New Modulation Technique and Performance Analysis," *IEEE Commun. Lett.*, vol. 17, no. 4, pp. 645–648, Apr. 2013.
- [3] A. Noel, K. Cheung, and R. Schober, "Optimal Receiver Design for Diffusive Molecular Communication with Flow and Additive Noise," *IEEE Trans. NanoBiosci.*, vol. 13, no. 3, pp. 350–362, Sept. 2014.
- [4] M. Mahfuz, D. Makrakis, and H. Mouftah, "A Comprehensive Study of Sampling-Based Optimum Signal Detection in Concentration-Encoded Molecular Communication," *IEEE Trans. NanoBiosci.*, vol. 13, no. 3, pp. 208–222, Sept. 2014.
- [5] G. Wei and R. Marculescu, "Miniature Devices in the Wild: Modeling Molecular Communication in Complex Extracellular Spaces," *IEEE J. Select. Areas Commun.*, vol. 32, no. 12, pp. 2344–2353, Dec 2014.
- [6] M. Moore, T. Nakano, A. Enomoto, and T. Suda, "Measuring Distance From Single Spike Feedback Signals in Molecular Communication," *IEEE Trans. Sig. Proc.*, vol. 60, no. 7, pp. 3576–3587, July 2012.
- [7] A. Noel, K. Cheung, and R. Schober, "Bounds on Distance Estimation via Diffusive Molecular Communication," in *IEEE Globecom*, Dec. 2014, pp. 2813–2819.
- [8] A. Akkaya, H. Yilmaz, C.-B. Chae, and T. Tugcu, "Effect of Receptor Density and Size on Signal Reception in Molecular Communication via Diffusion With an Absorbing Receiver," *IEEE Commun. Lett.*, vol. 19, no. 2, pp. 155–158, Feb. 2015.
- [9] A. Ahmadzadeh, A. Noel, A. Burkovski, and R. Schober, "Amplify-and-Forward Relaying in Two-Hop Diffusion-Based Molecular Communication Networks," *accepted for presentation in IEEE Globecom*, 2015.
- [10] M. Pierobon and I. Akyildiz, "A Physical End-to-End Model for Molecular Communication in Nanonetworks," *IEEE J. Sel. Areas Commun.*, vol. 28, no. 4, pp. 602–611, May 2010.
- [11] D. Miorandi, "A Stochastic Model for Molecular Communications," *Nano Commun. Netw.*, vol. 2, no. 4, pp. 205–212, 2011.
- [12] N. Farsad, A. Eckford, and S. Hiyama, "A Markov Chain Channel Model for Active Transport Molecular Communication," *IEEE Trans. Signal. Process.*, vol. 62, no. 9, pp. 2424–2436, May 2014.

- [13] A. Noel, K. Cheung, and R. Schober, "A Unifying Model for External Noise Sources and ISI in Diffusive Molecular Communication," *IEEE J. Sel. Areas Commun.*, vol. 32, no. 12, pp. 2330–2343, Dec. 2014.
- [14] A. Bicen and I. Akyildiz, "End-to-End Propagation Noise and Memory Analysis for Molecular Communication over Microfluidic Channels," *IEEE Trans. Commun.*, vol. 62, no. 7, pp. 2432–2443, July 2014.
- [15] S. Crozier, D. Falconer, and S. Mahmoud, "Least Sum of Squared Errors (LSSE) Channel Estimation," *IEE Proc. F Radar Sig. Process.*, vol. 138, no. 4, pp. 371–378, Aug 1991.
- [16] M. Ozdemir and H. Arslan, "Channel Estimation for Wireless OFDM Systems," *IEEE Commun. Surveys Tutorials*, vol. 9, no. 2, pp. 18–48, 2007.
- [17] C. Gong and Z. Xu, "Channel Estimation and Signal Detection for Optical Wireless Scattering Communication with Inter-Symbol Interference," *IEEE Trans. Wireless Commun.*, vol. PP, no. 99, pp. 1–1, 2015.
- [18] X. Zhang, C. Gong, and Z. Xu, "Estimation of NLOS Optical Wireless Communication Channels with Laser Transmitters," in *Proc. Asilomar Conf. Signals, Syst., Comput.*, Nov 2014, pp. 268–272.
- [19] A. Gelman, J. B. Carlin, H. S. Stern, and D. B. Rubin, *Bayesian Data Analysis*. Taylor & Francis, 2014, vol. 2.
- [20] S. Boyd and L. Vandenberghe, *Convex Optimization*. Cambridge, U.K.: Cambridge Univ. Press, 2004.
- [21] P. H. Schonemann, "On the Formal Differentiation of Traces and Determinants," *Multivariate Behavioral Research*, vol. 20, no. 2, pp. 113–139, 1985.