Theoretical Performance Bounds of Model-Based Electrocardiogram Parameter Estimation

Davood Fattahi and Reza Sameni*, *Senior Member, IEEE*

Abstract—Clinical parameter estimation from the electrocardiogram (ECG) is a recurrent field of research. It is debated that ECG parameters estimated by human experts and machines/algorithms is always *model-based* (implicitly or explicitly). Therefore, depending on the selected data-model, the adopted estimation scheme (least-squares error, maximum likelihood, or Bayesian), and the prior assumptions on the model parameters and noise distributions, *any* estimation algorithm used in this context has an upper performance bound, which is not exceedable (for the same model and assumptions).

In this research, we develop a comprehensive theoretical framework for ECG parameter estimation and derive the Cramér-Rao lower bounds (CRLBs) for the most popular signal models used in the ECG modeling literature, namely bases expansions (including polynomials) and sum of Gaussian functions. The developed framework is evaluated over real and synthetic data, for three popular applications: T-to-R wave ratio estimation, ST-segment analysis and QT-interval estimation, using the state-of-the-art estimators in each context, and compared with the derived theoretical CRLBs. The proposed framework and the derived CRLBs provide practical guidelines for the selection of data-models, sampling frequency (beyond the Nyquist requirements), modeling segment length, the number of beats required for average ECG beat extraction, and other factors that influence the accuracy of ECG-based clinical parameter estimation.

Index Terms—Electrocardiogram; parameter estimation; Cramér-Rao lower bound; electrocardiogram modeling; ECG fiducial points; sum of Gaussian model

I. INTRODUCTION

The electrocardiogram (ECG) is a rich source of information for cardiac diagnoses. For decades, a significant branch of biomedical research has been devoted to the reliable extraction of clinical parameters from the ECG. In recent years, new technologies such as wearable healthcare monitoring gadgets [1], ECG acquisition during stress-tests and sports [2], and noninvasive fetal ECG monitoring have emerged [3], which have once again brought about the necessity of accurate ECG parameter extraction, especially in edge-computing and highly noisy scenarios.

It can be debated that ECG annotation and parameter extraction are always implicitly or explicitly “model-based”. Expert human annotators use visual features such as local peaks, morphological variations, rhythms, level-crossings, slopes, intersections of curves, etc. These features are essentially based on mental or verbalized models of the ECG waveform, which are learned by experience and formalized in textbooks [4], [5]. Machine-based annotations are in turns either *structural*:

based on the same set of models and features used by humans and formalized in mathematical/algorithmic form [6], or *statistical*: based on novel machine learning (ML) techniques that feed the ECG (or its features), to a machine learning algorithm/network, which implicitly learns the data-model [7].

Mathematical models used for ECG annotations are rather diverse, among which polynomial expansions [8]–[10], and sum of Gaussian functions [11]–[13] are the most popular. Standard ECG annotation software use combinations and intersections of such models to define wave peaks, fiducial points, onsets, offsets, DC levels, durations, etc., which in turns are used for diagnostic purposes by experts and algorithms.

From the estimation theoretical perspective, model-based parameter estimation in presence of measurement noise and model inaccuracies has theoretical bounds, which may not be exceeded by *any* estimation scheme. The *Cramér-Rao lower-bound* (CRLB) is the most popular of such bounds, which imposes a lower bound on the mean square error of any estimator, for a presumed signal-noise model [14]. The estimation of ECG parameters (either by experts or machines) is not an exception, and to date, not many attempts have been made to formulate the theoretical bounds of this problem.

In this work, we study the problem of ECG parameter extraction from the estimation theoretical perspective and present a systematic approach to the estimation of arbitrary ECG parameters, and demonstrate how clinical ECG parameter estimation can be translated into a formal estimation problem.

Within this framework, we focus on the most popular models used in ECG parameter extraction, namely *linear-in-parameters* (specifically *polynomial expansions*), and *sum of Gaussians*. It is later shown how these models perform in least squares (LS), maximum likelihood (ML) and Bayesian frameworks, and demonstrate that although the selection of the data-model and estimation schemes are arbitrary (and application dependent), the choice has inevitable consequences on the attainable performance bounds, regardless of the algorithm used for parameter estimation. We specifically derive the CRLB for the most popular ECG models and present some common rules of thumb for improving the CRLB of ECG parameters. As case studies, the proposed framework is applied to problems of estimating T-to-R wave ratios, ST-segment analysis, and QT-interval estimation, using state-of-the-art ECG parameter estimators. The numeric estimation performance bounds are compared with the derived CRLB.

The results of this study are shown to have significant applications for computerized and non-computerized annotations and highlight the fact that ECG parameters should always be reported with confidence intervals, and are only valid within

*Department of Biomedical Informatics, School of Medicine, Emory University, 101 Woodruff Circle, Atlanta, GA 30322. email: rsameni@dbmi.emory.edu

the scope of the utilized ECG model and estimation scheme.

In Section II, the data model is presented. In Section III, the CRLB for well-known ECG models are derived, followed by practical extensions of the framework in Section IV. In Section V, several case studies are studied and the performance of different algorithms versus the derived CRLBs are compared on both real and synthetic data. A detailed discussion regarding the outcomes of this study is presented in Section VI. The paper is concluded with a summary and future perspectives in Section VII. The required estimation theoretical backgrounds are reviewed in the Appendix.

II. DATA MODEL

Standard ECG delineation software and computerized devices commonly follow similar steps for ECG analysis. This includes: 1) preprocessing (baseline-wander removal, powerline cancellation and out-of-band noise rejection); 2) R-peak detection and heart-rate time-series calculation; 3) ECG beat extraction; 4) morphological feature extraction from single or average beats [15]–[17]. The latter commonly consists of fitting a parametric model onto segments of the (average) beat.

Suppose that $x(t)$ denotes an ECG, an average beat or a *segment-of-interest* (SoI) of an ECG, at time t , modeled as

$$x(t) = \tilde{x}(t; \boldsymbol{\theta}) + e(t) \quad (1)$$

where $\tilde{x}(t; \boldsymbol{\theta})$ is a parametric model of the SoI, $\boldsymbol{\theta} \in \mathbb{R}^P$ is the model parameter vector and $e(t)$ is measurement noise. By sampling $x(t)$ at a frequency f_s ($T_s = 1/f_s$), we define $\mathbf{x} \in \mathbb{R}^N$ as the vectorized form of the N samples $x(nT_s)$ ($n = n_0, n_0 + 1, \dots, n_0 + N - 1$) starting at an initial time $t_0 = n_0 T_s$, $\tilde{\mathbf{x}}(\boldsymbol{\theta}) \in \mathbb{R}^N$ as the vectorized form of the model samples $\tilde{x}(nT_s; \boldsymbol{\theta})$, and $\mathbf{e} \in \mathbb{R}^N$ as the vector form of the measurement noise $e(nT_s)$, the vectorial equivalent of (1) is:

$$\mathbf{x} = \tilde{\mathbf{x}}(\boldsymbol{\theta}) + \mathbf{e} \quad (2)$$

The model parameters $\boldsymbol{\theta}$ are related to the clinical parameter of interest through some transformation. In both manual and computerized annotations, the clinical ECG parameters are commonly characterized in one of the following forms: 1) local peaks of the SoI; 2) an intersection point of two curves, or 3) amplitudes (or amplitude ratios) at some fiducial point. Mathematically, these conditions translate into an equation that relates a clinical parameter γ^* to the parameter vector $\boldsymbol{\theta}$:

$$\gamma^* = \arg_{\gamma} \{\phi(\boldsymbol{\theta}, \gamma) = 0\} = \mathcal{T}(\boldsymbol{\theta}) \quad (3)$$

where $\phi(\cdot, \cdot)$ is a function that relates the model and clinical parameters. For example, the R-peak is commonly identified as the global peak across the beat. Therefore, taking γ^* as the R-peak location and $\phi(\boldsymbol{\theta}, \gamma) \triangleq \frac{d}{dt} \tilde{x}(\boldsymbol{\theta}; t)$, γ^* is related to the model parameters vector by solving $\phi(\boldsymbol{\theta}, \gamma) = 0$ for γ . As another example, the onsets or offsets of the ECG components can be defined as the intersection of the baseline, modeled by a parametric function $b(t)$ (a horizontal line in the simplest case) and another model $\tilde{x}(\boldsymbol{\theta}; t)$ fitted over the SoI. Therefore, $\phi(\boldsymbol{\theta}, \gamma) \triangleq \tilde{x}(\boldsymbol{\theta}; t) - b(t)$, and its root $\gamma^* = \mathcal{T}(\boldsymbol{\theta})$ is the clinical parameter of interest. The notion of relating model parameters to clinical parameters can be extended to fiducial points, peak

amplitudes, segment lengths, etc., in all cases resulting in a transformation of the form $\gamma^* = \mathcal{T}(\boldsymbol{\theta})$ that relates the model and clinical parameter of interest.

Note that the existence of a unique solution for (3) is an implicit assumption of model-based ECG parameter extraction. Therefore, although $\phi(\boldsymbol{\theta}, \gamma) = 0$ might mathematically have multiple roots, the optimal γ^* is selected from constraints on the clinically admissible set of parameters (e.g., constraints such as the max/min ranges, sign, and width of the parameter).

A. Model parameters and noise distribution

The core of ML and Bayesian frameworks are the prior and posterior distributions of model parameter and noise. Beyond the powerline and device noises with known origin, other in-band ECG noises are to a very good extent Gaussian distributed [16, Ch. 3]. This is the most common assumption in advanced ECG modeling and denoising schemes such as Gaussian Process filters [18] and Extended Kalman filters [19]. The spectral color of the noise is however subjective. Therefore, in the sequel, we consider the general case $\mathbf{e} \sim \mathcal{N}(\mathbf{0}, \boldsymbol{\Sigma}_e)$. For Bayesian schemes, we further require the distribution of the parameter vector $\boldsymbol{\theta}$, which is subjective (depends on the parameter of interest). For the later studied case-studies, we consider $\boldsymbol{\theta} \sim \mathcal{N}(\boldsymbol{\mu}_{\boldsymbol{\theta}}, \boldsymbol{\Sigma}_{\boldsymbol{\theta}})$ [20]. However, the proposed framework is generic and as shown in the Appendix, following (32), arbitrary parameter priors can be used whenever available. More generally, the effect of model mismatch can also be incorporated in the extracted CRLBs [21].

III. CRAMÉR-RAO LOWER BOUNDS OF COMMON ECG MODELS

In this section, we derive the ML CRLBs for *linear-in-parameters* and *sum-of-Gaussian* expansions, as the most popular ECG (or ECG segment) models. The required estimation theoretical backgrounds are provided in the Appendix.

A. Linear-in-parameter functional expansions

Linear-in-parameter models can be formulated as

$$\tilde{x}(nT_s; \boldsymbol{\theta}) = \sum_{i=1}^P \theta_i h_i(nT_s) = \mathbf{h}(nT_s)^T \boldsymbol{\theta}, \quad (4)$$

where $\mathbf{h}(nT_s) = [h_1(nT_s), h_2(nT_s), \dots, h_P(nT_s)]^T$ ($n = n_0, \dots, n_0 + N - 1$) is the vector of elements (spanning set) and $\boldsymbol{\theta} = [\theta_1, \theta_2, \dots, \theta_P]^T$ denotes the vector of parameters. We are specifically interested in families of $\mathbf{h}(nT_s)$, which form a *basis* for the sampled ECG signal space. This guarantees that “any” ECG would have an expansion in the form of (4) and there exists a parameter vector $\boldsymbol{\theta}$, which satisfies this equation. Since the ECG is a finite energy signal (both in continuous and sampled spaces), arbitrary basis expansions for the Hilbert space can be used in this context. Using (28) and (34), the Fisher Information for linear-in-parameter models is obtained:

$$\mathcal{I}_{\text{ML}}(\boldsymbol{\theta}) = \frac{1}{\sigma_e^2} \sum_{n=n_0}^{n_0+N-1} \mathbf{h}(nT_s) \mathbf{h}(nT_s)^T. \quad (5)$$

Specifically, if $\mathbf{h}(\cdot)$ form an orthonormal basis, they satisfy $\sum_{n=n_0}^{n_0+N-1} \mathbf{h}(nT_s) \mathbf{h}(nT_s)^T = N\mathbf{I}$, resulting in $\mathcal{I}_{\text{ML}}(\boldsymbol{\theta}) = \frac{N}{\sigma_e^2} \mathbf{I}$.

As a special case, polynomials and monomials are the simplest form of linear expansions used for ECG segment modeling [22], [23]. In (4), setting $h_i(t) = t^{i-1}$ results in

$$\tilde{x}(nT_s; \boldsymbol{\theta}) = \theta_1 + \theta_2 \cdot (nT_s) + \dots + \theta_P \cdot (nT_s)^{P-1}. \quad (6)$$

Letting $\mathbf{h}(nT_s) = [1, nT_s, \dots, (nT_s)^{P-1}]^T$, the Fisher Information is obtained from (5).

B. Sum of Gaussian functions

Sum of Gaussian (SoG) functions are very common in ECG modeling [11]. Due to their morphological similarity with the ECG components, the ECG can be accurately modeled with a few Gaussians. Although SoG functions are neither orthogonal nor linear-in-all-parameters, they form a *frame* for *energy signals* [24]. Moreover, due to the similarity of the ECG components with Gaussians, the model parameters can be related to clinical ECG parameters by simple transforms [13]. A SoG model can be used to synthesize a beat or segment of an ECG as follows:

$$\tilde{x}(nT_s; \boldsymbol{\theta}) = \sum_{i=1}^M g_i(nT_s) = \sum_{i=1}^M a_i \exp\left(-\frac{(nT_s - c_i)^2}{2b_i^2}\right), \quad (7)$$

where $\boldsymbol{\theta} = [a_1, b_1, c_1, \dots, a_M, b_M, c_M]^T$ is the parameter vector, $g_i(nT_s)$ denotes the Gaussian functions, and in accordance with our original data-model (1), $M = P/3$ is the number of Gaussian functions, with peak amplitude a_k , effective width b_k and centered at c_k . Equation (7) is linear in the Gaussian amplitudes and nonlinear in the center and width parameters.

For this model, the Fisher Information matrix $\mathcal{I}_{\text{ML}}(\boldsymbol{\theta}) \in \mathbb{R}^{3M \times 3M}$ consists of M sub-matrices corresponding to each of the Gaussians:

$$[\mathcal{I}_{\text{ML}}(\boldsymbol{\theta})]_{ij} = \begin{pmatrix} \mathcal{I}_{a_i a_j} & \mathcal{I}_{a_i b_j} & \mathcal{I}_{a_i c_j} \\ \mathcal{I}_{b_i a_j} & \mathcal{I}_{b_i b_j} & \mathcal{I}_{b_i c_j} \\ \mathcal{I}_{c_i a_j} & \mathcal{I}_{c_i b_j} & \mathcal{I}_{c_i c_j} \end{pmatrix}, \quad i, j = 1, 2, \dots, M \quad (8)$$

Using (34) and defining $\Delta_i(n) \triangleq (nT_s - c_i)$, the elements of the Fisher Information matrix are found as follows

$$\begin{aligned} \mathcal{I}_{a_i a_j} &= \frac{1}{\sigma_e^2} \sum_{n=n_0}^{n_0+N-1} \frac{1}{a_i a_j} g_i(nT_s) g_j(nT_s) \\ \mathcal{I}_{b_i b_j} &= \frac{1}{\sigma_e^2} \sum_{n=n_0}^{n_0+N-1} \frac{\Delta_i(n)^2 \Delta_j(n)^2}{b_i^3 b_j^3} g_i(nT_s) g_j(nT_s) \\ \mathcal{I}_{c_i c_j} &= \frac{1}{\sigma_e^2} \sum_{n=n_0}^{n_0+N-1} \frac{\Delta_i(n) \Delta_j(n)}{b_i^2 b_j^2} g_i(nT_s) g_j(nT_s) \\ \mathcal{I}_{a_i b_j} &= \frac{1}{\sigma_e^2} \sum_{n=n_0}^{n_0+N-1} \frac{\Delta_j(n)^2}{a_i b_j^3} g_i(nT_s) g_j(nT_s) \\ \mathcal{I}_{a_i c_j} &= \frac{1}{\sigma_e^2} \sum_{n=n_0}^{n_0+N-1} \frac{\Delta_j(n)}{a_i b_j^2} g_i(nT_s) g_j(nT_s) \\ \mathcal{I}_{b_i c_j} &= \frac{1}{\sigma_e^2} \sum_{n=n_0}^{n_0+N-1} \frac{\Delta_i(n)^2 \Delta_j(n)}{b_i^3 b_j^2} g_i(nT_s) g_j(nT_s). \end{aligned} \quad (9)$$

1) *Full-wave segregated Gaussian fitting*: In deriving (9) we have made no assumptions on the number or center of the Gaussian functions. These equations can be simplified to obtain tangible rules of thumb regarding the Fisher Information of the well-distanced Gaussian functions (e.g., corresponding to the P, QRS, and the T-waves of the ECG). Specifically, if

- (i) the Gaussians are well-distanced as compared with their effective widths, i.e. $(c_i - c_j)^2 \gg (b_i^2 + b_j^2)$ ($i \neq j$),
- (ii) the signal is significantly over-sampled, i.e. $f_s \gg 2f_{\text{max}}$, where f_s and f_{max} are respectively the sampling and the maximum frequencies of the signal (permitting the summations to be approximated by Riemann integrals),
- (iii) the SoI covers the effective segments of all the Gaussian functions (summation of the Gaussian residuals outside the SoI can be neglected),

then for $i \neq j$, $[\mathcal{I}_{\text{ML}}(\boldsymbol{\theta})]_{ij} \approx 0$, $[\mathcal{C}_{\text{ML}}(\boldsymbol{\theta})]_{ij} \approx 0$ and for $i = j$, the following approximations hold:

$$[\mathcal{I}_{\text{ML}}(\boldsymbol{\theta})]_{ii} \approx \frac{\sqrt{\pi}}{T_s \sigma_e^2} \begin{pmatrix} b_i & \frac{a_i}{2} & 0 \\ \frac{a_i}{2} & \frac{3a_i^2}{4b_i} & 0 \\ 0 & 0 & \frac{a_i^2}{2b_i} \end{pmatrix}, \quad (10)$$

$$[\mathcal{C}_{\text{ML}}(\boldsymbol{\theta})]_{ii} \approx \frac{T_s \sigma_e^2}{\sqrt{\pi}} \begin{pmatrix} \frac{3}{2b_i} & -\frac{1}{a_i} & 0 \\ -\frac{1}{a_i} & \frac{2b_i}{a_i^2} & 0 \\ 0 & 0 & \frac{2b_i}{a_i^2} \end{pmatrix}. \quad (11)$$

2) *Half-wave Gaussian fitting*: Half-wave Gaussians have been shown to be useful for modeling asymmetric ECG waves such as the P- and T-wave [13], [25]. Suppose that a Gaussian function is used to model a half-wave ECG, under similar conditions listed in Section III-B1, the Gaussians significantly dwindle outside the modeled SoI. Therefore, for $i \neq j$, $[\mathcal{I}_{\text{ML}}(\boldsymbol{\theta})]_{ij} \approx 0$, $[\mathcal{C}_{\text{ML}}(\boldsymbol{\theta})]_{ij} \approx 0$ and for $i = j$, we obtain

$$[\mathcal{I}_{\text{ML}}(\boldsymbol{\theta})]_{ii} \approx \frac{\sqrt{\pi}}{2T_s \sigma_e^2} \begin{pmatrix} b_i & \frac{a_i}{2} & \frac{a_i}{\sqrt{\pi}} \\ \frac{a_i}{2} & \frac{3a_i^2}{4b_i} & \frac{a_i^2}{\sqrt{\pi} b_i} \\ \frac{a_i}{\sqrt{\pi}} & \frac{a_i^2}{\sqrt{\pi} b_i} & \frac{a_i^2}{2b_i} \end{pmatrix}, \quad (12)$$

$$[\mathcal{C}_{\text{ML}}(\boldsymbol{\theta})]_{ii} \approx \frac{2T_s \sigma_e^2}{\sqrt{\pi}(\pi - 3)} \begin{pmatrix} \frac{3\pi-8}{2b_i} & -\frac{4-\pi}{a_i} & -\frac{\sqrt{\pi}}{a_i} \\ -\frac{4-\pi}{a_i} & \frac{2(\pi-2)b_i}{a_i^2} & -\frac{2\sqrt{\pi}b_i}{a_i^2} \\ -\frac{\sqrt{\pi}}{a_i} & -\frac{2\sqrt{\pi}b_i}{a_i^2} & \frac{2\pi b_i}{a_i^2} \end{pmatrix}. \quad (13)$$

From (10)-(13), as long as the SoI covers the entire modeled wave (the requirement for approximating (9) with (10)), the centers of the Gaussian functions do not appear in the CRLB bounds. The practical implications of the Fisher Information and CRLBs are later discussed in the results and discussions.

IV. PRACTICAL EXTENSIONS

A. Performance bounds on clinical parameter estimation

The CRLB of the mathematical model parameters can be transformed to CRLBs on the clinical parameters. Following the background in Section II, if $\gamma = \mathcal{T}(\boldsymbol{\theta})$ denotes the mapping between the model and clinical parameters, the ML CRLB of γ is obtained as follows [14],

$$\mathcal{C}_{\text{ML}}(\gamma) = \left(\frac{\partial \mathcal{T}}{\partial \boldsymbol{\theta}}\right)^T \mathcal{C}_{\text{ML}}(\boldsymbol{\theta}) \left(\frac{\partial \mathcal{T}}{\partial \boldsymbol{\theta}}\right), \quad (14)$$

The same equation holds for the CRLB in the Bayesian framework. While $\gamma = \mathcal{T}(\theta)$ might not be (generally) available in analytical form (due to a non closed-form solution for (3)), by using Sequential Monte Carlo techniques, the CRLB of the model vs clinical parameters can be numerically calculated through numeric approximations of the gradient in (14).

B. CRLB in multi-beat estimation

ECG parameter estimation from more than one beat is a common technique to obtain more accurate parameter estimates. Many ECG analysis software use an average, weighted average, or median of multiple beats to form a ‘template beat’ used for estimating parameters such as the QRS width, QT interval, etc. [26]. The R-peak is commonly used as the reference point for aligning the multiple beats. The basic assumption is that the ECG morphology is rather consistent and the ECG deviations and noise are uncorrelated across the beats. Under these conditions, it has been shown that the signal-to-noise ratio (SNR) of the template beat is improved by a factor K , by synchronous averaging over K beats [27]. Regardless of the estimation algorithm (averaging, weighted averaging, median, etc.), we show how using multiple beats generally improves the CRLB.

Extending the data-model in (2) to multiple beats, we denote each ECG beat (or segment of interest) of length N as

$$\mathbf{x}^{(k)} = \tilde{\mathbf{x}}(\theta) + \mathbf{e}^{(k)}, \quad k = 1, \dots, K \quad (15)$$

where $\mathbf{e}^{(k)}$ is the beat/segment noise, and all K beats/segments share the same signal model $\tilde{\mathbf{x}}(\theta)$ parameterized by the parameter vector θ (deterministic or stochastic). Next, let $\mathcal{X} = \{\mathbf{x}^{(k)}\}_{k=1}^K$ be the set of all K beats. If the noises of the ECG beats are stochastically independent, we have

$$f(\mathcal{X} | \theta) = \prod_{k=1}^K f_{e_k}(\mathbf{x}^{(k)} - \tilde{\mathbf{x}}(\theta)) \quad (16)$$

where $f_{e_k}(\cdot)$ denoted the pdf of the noise in beat/segment k . Therefore, the Fisher Information of $\mathcal{X}$ equates

$$\mathcal{I}_{\text{ML}}^{(\mathcal{X})}(\theta) = \sum_{k=1}^K \mathcal{I}_{\text{ML}}^{(k)}(\theta) \quad (17)$$

where $\mathcal{I}_{\text{ML}}^{(k)}(\theta)$ denotes the ML Fisher Information of beat/segment k . Specifically, if $\mathbf{e}^{(k)} \sim \mathcal{N}(\mathbf{0}, \Sigma_{e_k})$ we obtain

$$\mathcal{I}_{\text{ML}}(\theta) = \frac{\partial \tilde{\mathbf{x}}(\theta)}{\partial \theta}^T \left(\sum_{k=1}^K \Sigma_{e_k}^{-1} \right) \frac{\partial \tilde{\mathbf{x}}(\theta)}{\partial \theta}, \quad (18)$$

which is a multi-beat generalization of (34). The same result extends to the Bayesian Fisher Information. From (18), it is apparent that involving more observations (beats) can improve the performance bound of estimation for the underlying parameter of interest. As a special case, if the covariance matrices of the additive noise are the same for all the K beats/segments, the Fisher Information in multi-beat experiment is exactly K times the single-beat estimation case.

Fig. 1. A sample multichannel ECG beat superposed. Notice the similarities and differences in the clinical parameters of the ECG across all channels.

C. CRLB for multichannel ECG

The heart is a spatially distributed signal source. Therefore, multi-lead ECG (commonly between six to twelve leads) is very common in clinical trials and each ECG channel is best used for measuring a specific cardiac activity. A state-of-the-art question is “*how many and which ECG channels are most informative for extracting clinical ECG parameters?*” [28]. As shown in Fig. 1, while there is a lot of shared information between different ECG channels, there are also significant differences between the channel-wise waveforms.

To set up a model-based multichannel ECG parameter extraction framework, one can model each channel independently and fuse the model parameters of each channel in the overall clinical parameters at a second step. To extend the data-model in (2) to L -channel recordings, we denote:

$$\mathbf{x}_l = \tilde{\mathbf{x}}_l(\theta_l) + \mathbf{e}_l, \quad (l = 1, \dots, L) \quad (19)$$

where $\tilde{\mathbf{x}}_l(\theta_l)$ is the signal model in channel l , parameterized by the parameter vector $\theta_l \in \mathbb{R}^{P_l}$ with P_l parameters per-channel, and $\mathbf{e}_l$ is the noise vector in channel l (notice the notation difference with the multi-beat model in (15)). Next, extending (3) to multichannel, the clinical parameter of interest is related to the channel-wise parameters in vector form:

$$\gamma^* = \arg_{\gamma} \{\Phi(\theta_1, \dots, \theta_L, \gamma) = 0\} = \mathcal{T}(\theta_1, \dots, \theta_L) \quad (20)$$

where $\Phi(\cdot)$ relates multi-lead parameters with the clinical parameter of interest.

Note that in real-world multi-channel ECG, the per-channel model parameters θ_l and ECG noise in different channels are rarely independent across the channels. Therefore, the total multichannel Fisher Information is not additive as in the single-channel multi-beat case derived in (17), and the derivation of the CRLB requires per-model customization.

V. CASE STUDIES

A. Model-based T/R amplitude ratio calculation

In LS schemes, due to the lack of priors and posteriors, the CRLB is not defined. Nevertheless, even without priors and posteriors, a (justifiable) model-based approach outperforms non-model-based ones. As a first case study, we show how a model-based approach to parameter estimation significantly improves the accuracy in ECG parameter estimation.

Fig. 2. A noisy ECG beat and the two polynomial models of order $M=6$ fitted over the R- and T-waves.

The T-to-R wave amplitude ratio (known as the T/R ratio) is an important clinical index in ECG-based studies [29]. The calculation of the ratio in noisy data can be very challenging. The direct approach for calculating the T/R ratio, is to detect the local R- and T-wave peaks and to calculate their ratios. A more robust approach is to fit a parametric model over the ECG segments corresponding to the QRS and the T-waves and to calculate the T/R ratio from the fitted model. For this purpose we adopt a polynomial model of order P using (6). To calculate the T/R ratio, we fit two separate models over the QRS and T-waves and the model coefficients are obtained from (35), using the LS scheme (or an ML scheme with Gaussian noise assumption). In Fig. 2, a typical noisy ECG and the models fitted over the QRS and T segments are shown. The model order was empirically set to $P=6$ for this example and the QRS and T-wave models were fitted over windows of lengths 50 ms and 250 ms around the QRS and T-wave peaks, respectively. For a statistical study, 627 ECG beats recorded from different channels were randomly selected from the PTB Diagnostic ECG Database [30]. White Gaussian noise (WGN) with an SNR of 10 dB was added to each beat and the T/R amplitude ratios were calculated from the original and noisy beats, with and without polynomial model fitting.

In Fig. 3, the scatter plots of the T/R ratios are compared between the original and noisy beats, with and without model fitting. Apparently, the results with polynomial model fitting are much better aligned along the identity line. Statistically, the Spearman's correlation (ρ) increased from 0.57 to 0.97 after using the model-based approach, which indicates that the model has made the calculation more robust to noise. The Spearman's correlation was also calculated for a sweep of SNR ranging from 0 dB to 30 dB in 2 dB steps, as shown in Fig. 3(d), which demonstrates the significance of using a model-based approach (especially in low SNR).

B. ST-segment parameter estimation using polynomials

The ST-segment and its morphological properties contain significant clinical information regarding heart defects such as myocardial ischaemia or infarction. The ST-segment is a relatively smooth and close to flat segment of the ECG, enabling its modeling with low-order polynomials. The coefficients of the zero-, first- and second-order polynomials have been

associated with level, slope and scooping of the ST-segment, respectively, which are clinically informative [31].

The ST-level is commonly obtained by selecting a specific point from the ST-segment [32] (or for better robustness, an average of a few points/segment of the ST-segment [33]–[35]). This corresponds to estimating the DC level (average) of the ST segment. To find the appropriate sample, or range of samples for averaging, the estimator needs some *fiducial points* as reference, which are commonly obtained relative to landmarks such as the R-peak, the J-point (end of S-wave), etc. Therefore, these methods use the same data-model, in which a zero-order polynomial (a horizontal line) is fit to the ST-segment. More advanced methods, use non-zero-slope line fits or higher order polynomials, which provide additional clinical parameters such as the ST-slope and the ST-index [32], [36].

1) *Theoretic CRLB*: For this experiment, the ST-segment is modeled by a line. If the center of SoI is chosen as the reference time $t = 0$, the ST-level and ST-slope correspond to the DC (θ_0) and slope (θ_1) parameters of the line. The CRLBs for these parameters are obtained from (5) and (6). Previous research have defined the *ST-index* $i_{ST} = \theta_0 + \beta\theta_1$, which is a linear regression between the two parameters with the slope parameter β (found by model fitting over large datasets), and shown that it can be used as a useful clinical parameter [32], [36]. Following (14), the CRLB for the ST-index is

$$\mathcal{C}(i_{ST}) = \begin{bmatrix} 1 & \beta \end{bmatrix} \mathcal{C}(\theta) \begin{bmatrix} 1 \\ \beta \end{bmatrix}^T. \quad (21)$$

Since the SoI was assumed to be centered at $t = 0$, we can show that the first order polynomial bases functions are orthogonal, and therefore $\mathcal{C}(\theta)$ is diagonal. Therefore, the CRLB of θ_0 and θ_1 can be studied independently and the CRLB of i_{ST} simplifies to $\mathcal{C}(i_{ST}) = \mathcal{C}(\theta_0) + \beta^2 \mathcal{C}(\theta_1)$.

2) *Real dataset*: The PhysioNet Long-Term ST Database was used for evaluation this case study [37]. The dataset consists of 86 ECG records from 80 subjects with a variety of ST-segment variations. Each record is between 21 and 24 hours long and contains two to three ECG signals sampled at 250 Hz. 100,000 beats were randomly selected from lead II (the most common lead in ST-segment analysis) from all subjects. The signal baselines were removed for further processing.

3) *Synthetic dataset*: For quantitative evaluations, in addition to the real dataset, the McSharry-Clifford sum of Gaussians (SoG) ECG model is used for synthetic ECG generation [11]. The model parameters were trained over the PTB Diagnostic ECG Database [38], by using the open-source electrophysiological toolbox (OSET) [39]. Accordingly, the ECG beats of lead II were segmented, mapped to the *cardiac phase domain* through R-peak alignment [40], and the average beat was calculated from the aligned beats. The R-peaks were considered as the reference time and the initial values of the SoG parameters were estimated by fitting the model on the average beat by nonlinear least squares. 26 subjects of the PTB dataset were chosen to generate a diverse collection of synthetic ECG types. The number of Gaussians used for ECG modeling varied for each subject and was chosen to achieve a normalized mean squares error below 0.02%.

Next, each of the 26 fitted models were used to generate synthetic two-minute ECGs. The center, amplitude, and width

Fig. 3. T/R ratio parameter estimation accuracy, with and without least-squares modeling. (a) T/R ratio histogram and comparison of T/R ratio alignment (b) before and (c) after polynomial model fitting for 627 ECG beats at SNR=10 dB; (d) The T/R ratio Spearman's correlation (ρ) in different SNR, with and without model fitting. Notice the alignment of the actual and estimated T/R ratio using the model-based scheme.

Fig. 4. A 10 s synthetic ECG generated by the SoG model with initial parameters trained over the PTB dataset and 3% relative deviation in the parameters (per-beat), and 4% relative deviation in the RR intervals, contaminated by white noise at a 22 dB SNR.

Fig. 5. Modeling the ST-segment by a first-order polynomial. The J-point is the common reference point for ST-segment localization, and the SoI ends after 60-80 ms, before the T-wave onset.

parameters of the Gaussians used for modeling each beat were chosen by random deviations around the initial fitted values per beat. The distribution of the deviated parameters were Normal, with a mean value of the initial values (obtained from the model fitting process) and a 3% relative standard deviation (RSTD). This approach preserves the R-peak centers unchanged (since the R-peaks are assumed to be at $t = 0$ of the SOI), while the centers of the Gaussians used for the P- and T-waves undergo more variations, resulting in realistic ECG. The RR-intervals of the synthetic ECG were also Normal distributed, with the same mean value as the corresponding PTB data used for model training and RSTD of 4%. Fig. 4 shows 10 s of a synthetic ECG generated by this method.

4) *Simulation Scenario:* After removing the baseline, the ECG (real or synthetic) were segmented into beats. For each beat the SoI was chosen as a 60 ms segment starting from the J-point, as illustrated in Fig. 5. For the real data, the J-points were obtained from the PhysioNet annotation file, and for the synthetic ECG it was fixed to 40 ms after the R-peak. Next, the linear model coefficients were estimated by a LS fit over the clean ST-segments (before adding noise at different SNR levels), using (35). The same procedure was repeated for all the beats, to obtain the prior distribution of the linear model parameters from the clean signals. Next, the signals were contaminated by additive noise at different SNRs from -20 dB to 40 dB in 5 dB steps. The LS model fitting procedure was repeated for each noisy beat, to obtain the ST-segment DC and slope parameters. As a clinical parameter of interest, we also calculated i_{ST} numerically and compared it with the

theoretical CRLB in (21), for $\beta = 0.1$ as proposed in [32]. The ML and Bayesian estimates were next obtained from (35) and (37). Finally, the covariance of error between the parameters obtained from the noiseless and noisy records were calculated. This procedure was repeated three times per each ECG beat, each time with a different ensemble of the additive noise.

5) *Results:* The theoretical CRLB of the ML and Bayesian frameworks were separately obtained from the derivations in Section III. Fig. 6 demonstrates the CRLBs vs the experimental variances of error for the ST-level, ST-slope and ST-index of synthetic and real data, over different SNR. Accordingly, since the model is linear and the estimator is *efficient*, the ML estimator has reached the CRLB in all cases. However, for the real data in low SNR, there is a gap between the experimental variance of error and the CRLB of the Bayesian scheme, which is due to the inaccurate prior distribution, as later discussed in Section VI. For reference, in previous research the mean absolute error of ST-level estimation using different estimators is reported between $67.59 \mu\text{V}$, and $86.11 \mu\text{V}$ [41], which are above but in the same order of magnitude as the CRLBs calculated in Fig. 6(a) and 6(d), in typical SNRs.

C. QT-interval parameter estimation using Gaussian functions

The QT-interval is one of the most informative features of the ECG for coronary artery disease identification [42]. It is defined as the difference between the Q-wave onset and the T-wave offset, as shown in Fig. (7). For sum of Gaussian models,

Fig. 6. Variances of error compared with the theoretical CRLB for a polynomial model of the ST-segment and the corresponding ST-index.

Fig. 7. By using a Gaussian model, the QT interval is expressed as a function of the Gaussian function parameters fit on the Q- and T-waves.

the onset and offset of the Q and T-waves have been directly inferred from the model parameters [13], [43], [44].

1) *Theoretic CRLB*: Suppose that $\theta_Q = (a_Q, b_Q, c_Q)^T$ and $\theta_T = (a_T, b_T, c_T)^T$ are the parameter vectors of the amplitudes, widths and centers of the Gaussians by which the Q- and T-waves are modeled. The “effective width” of the Q- and T-waves is proportional to the Gaussian model widths, i.e., βb_Q and βb_T , where β is a constant factor [13]. In the sequel, we follow [13] by selecting $\beta = 3$, which equates setting the onsets/offsets at the point where the amplitude of the Gaussian falls below 98.9% of its maximum.

As shown in Fig. 7, the Q-wave onset (s_Q) and the T-wave offset (e_T) can be expressed as linear transforms of the Gaussian model parameters: $s_Q = c_Q - \beta b_Q$ and $e_T = c_T + \beta b_T$. The CRLBs of these parameters can be calculated from (14):

$$\begin{aligned} \mathcal{C}(e_T) &= [0 \ \beta \ 1] \mathcal{C}(\theta_T) [0 \ \beta \ 1]^T \\ \mathcal{C}(s_Q) &= [0 \ -\beta \ 1] \mathcal{C}(\theta_Q) [0 \ -\beta \ 1]^T \end{aligned} \quad (22)$$

Moreover, since by definition the QT-interval is $d_{QT} = e_T - s_Q$, the CRLB of the QT-interval is found as follows

$$\mathcal{C}(d_{QT}) = \mathcal{C}(e_T) + \mathcal{C}(s_Q), \quad (23)$$

where we have assumed that the parameters of the Gaussians fit over the Q- and T-waves are independent (a reasonable assumption due to their time gap).

2) *Real dataset*: The PhysioNet QT Database is used for this case study [45]. The dataset consists of over 100 fifteen-minute two-lead ECG recordings gathered from different databases with a wide variety of ECG morphologies, and sampled at 250 Hz. After baseline wander removal, 40,000 beats were randomly selected from all subjects for this study. The procedure for generating synthetic ECG for the QT-interval parameter estimation is exactly identical to the procedure detailed in Section V-B3.

3) *Simulation Scenario*: The ECG (real and synthetic) were first segmented into beats by using the R-peaks as landmark. The SoI for the Q-wave was set to the interval $[r - 80 \text{ ms}, r - 20 \text{ ms}]$, where r is the R-peak position in time. For the T-wave, the SoI was set to $[T_{\max} - 20 \text{ ms}, r + 0.6RR]$, where RR is the beat-wise RR-interval, and $T_{\max} = \arg \max_t x(t)$; $t \in [r + 80 \text{ ms}, r + 0.6RR]$. These ranges were adopted from related research on ECG beat segmentation [25], [46], [47].

The next step was to estimate the parameters from the clean ensembles. The SoG model was fitted on each of the SoI by applying the nonlinear LS in (24). The estimated parameters were used to calculate prior distributions of the model parameters. The clean ensembles were next contaminated by white Gaussian noise with an SNR range between -20 dB and 40 dB, in 5 dB steps. Having both the prior and posterior distributions, the ML and Bayesian CRLBs were calculated from (26).

The noise-contaminated signals were given to the nonlinear MAP and ML estimators detailed in Appendix B to estimate the SoG model parameters. The simulation was repeated three times per beat and per SNR, with different random additive noise to achieve more robust numeric results. Finally, the variances of error were compared with the theoretical CRLBs.

4) *Results*: Fig. 8 shows the square root of the CRLBs compared with the STD of error for the Q-wave onset, T-wave offset, and the QT-interval, estimated by a Gaussian model fit on the Q- and T-waves, for both the real and synthetic datasets. For the ML scheme, the Fisher Information $\mathcal{I}_{\text{ML}}(\gamma)$ is a function of the parameters. Therefore, to make visual comparison of the different methods feasible, the inverse of $\mathbb{E}_{\gamma}\{\mathcal{I}_{\text{ML}}(\gamma)\}$ is plotted in the results. From Fig. 8, it is seen that since the data-model is nonlinear in parameters and the estimators are not *efficient*, the performance has not reached the CRLB. Nonetheless, the CRLB still gives us an idea about the quality of the estimator and how close it is to the lower bound of error (per SNR). Moreover, the Q-wave onset and the T-wave offset do not have identical CRLBs. Therefore, the achievable lower error bound of the QT-interval is dominated by the error of one of the endpoints (not both).

The performance of the state-of-the-art QT-interval estimators are not far from the CRLB ranges calculated in the present study. For the same QT database, the Q-onset has been reported to have an STD of 7.7 ms [47], 8.6 ms [6], 9.2 ms [17], 8.5 ms [48], 4.3 ms [49], and 7.2 ms [50]. In the same studies, the T-wave offsets have been reported to have an STD of 18.1 ms, 27 ms, 30.3 ms, 15.6 ms, 20.3 ms, 15 ms and 18.6 ms, respectively. Referring to Fig. 8, these values are above the CRLB in the typical SNR range.

VI. DISCUSSION

The CRLB depends on the data-model and data-models are subjective and a matter of debate. Therefore, the CRLB by itself does not make any judgment about the validity of a model. However, different measures exist for model assessment, including the MSE between real data and the model, the Akaike information criterion (AIC), minimum description length (MDL), and goodness of fit analysis on the estimation results (to assess the prior and posterior assumptions). This makes the hereby derived CRLB a practical reference for evaluating human or machine-based ECG annotation system.

In the context of estimation theory, the CRLB is one of the many lower bounds of estimation error, and does not necessarily guide us towards an *efficient estimator*. However, when the estimator is efficient, the CRLB is indeed a gauge for the estimation accuracy. Moreover, regardless of the estimator efficiency, the CRLB provides helpful information regarding the appropriateness of the estimation scheme. In the sequel, we review some of the important results of this study, for the ECG models studied in Section III.

- 1) *Multi-beat parameter estimation*: From (17) and (18), for consistent (but not necessarily normal) ECG morphologies, synchronous averaging across multiple beats improves the performance bound by a factor K .
- 2) *SNR effect*: It is trivially expected that parameter estimation performance degrades in lower SNRs. This is confirmed in

all the Fisher Information equations in Section III, where σ_e^2 appears in the ML Fisher Information denominator. The SNR effect is also seen in the results in Figs. 6 and 8.

- 3) *Sampling rate and segment length*: There are generally three factors that influence the performance of the temporal ECG parameters such as peaks, onsets, offsets, and durations: A) the duration of the physical parameter of interest (in seconds), B) the length of the segment used for model fitting (in seconds), and C) the sampling frequency of the signal (in Hz). Although the three aspects are related, they do not have identical effects on the CRLB. Among these factors, following (5) and (10)-(13), the Fisher Information (CRLB) is linearly proportional to the sampling frequency (the sampling time). Therefore, as a rule of thumb, over-sampling above the Nyquist frequency generally improves the CRLB regardless of the other factors. The impact of factors (A) and (B) above, are less explicit. Looking at the entries (2, 2) and (3, 3) of the Fisher Information and CRLB matrices of the SoG model in (10)-(13), we notice that the CRLB (Fisher Information) is proportional (inversely proportional) to the effective width of the Gaussian model. Therefore, the rule of thumb is that the estimation error variance of ECG wave centers and widths is smaller (larger) for narrower (wider) waves. As an example, suppose that one has an efficient estimation algorithm that reaches the CRLB. At identical sampling rates and with sufficiently large segments, fitting a single Gaussian function over the QRS is more accurate than fitting a Gaussian over the T-wave. Moreover, since the SoI length does not appear in (10)-(13), we conclude that increasing the width of the SoI beyond the “effective width” of the parameter of interest does not improve the CRLB. This finding is approved in the QT-interval results in Fig. 8, where the CRLB for the Q-wave onset is smaller than the CRLB of the T-wave offset. Therefore, while the QT (or QTc) interval is considered as a clinical index, the beginning and end points of this interval have different lower bounds of estimation error. A practically important implication of this finding is that “for an accurate estimation of the QT (or QTc) interval, the Q-wave onset and T-wave offsets should be studied separately” (for instance using different data models, or with different weights); otherwise the CRLB of the QT-interval is dominated by the T-wave offset accuracy.
- 4) *Model parameter priors*: Comparing the ML and Bayesian frameworks, the term due to model parameter priors appears as an additive term in the Bayesian Fisher Information in (32). Since the Fisher Information is a positive definite matrix, accurate priors always decrease the CRLB (improve the performance bound). The results in Section V also approve this fact, where the Bayesian CRLB is always lower than the ML. However, the outperformance of the Bayesian vs ML estimation is only guaranteed for “accurate priors.” For example, since there were a considerable number of abnormal beats in the QT database, the assumption of Gaussian distributed priors for the model parameters were not accurate. Therefore, in Figs. 8(a) and 8(b) it is seen that the Bayesian performance is worse than ML in high SNRs, i.e., the priors have not helped to improve the

Fig. 8. Comparison of estimation performance and CRLB of QT-interval parameters from real and synthetic ECG, by fitting Gaussian functions on the Q- and T-waves. The standard deviation of the estimation error is compared with the square root of the theoretical CRLB.

estimation performance. However, for the synthetic data, where the parameters were synthetically generated by a normal distribution, the performance of the Bayesian and ML schemes are asymptotically identical in high SNRs (cf. Figs. 8(d) and 8(e)). A similar effect is seen for the real vs synthetic ST results in Fig. 6, where the Bayesian estimator is no longer reaches the CRLB (is non-efficient), when provided with inaccurate priors.

- 5) *Linear-in-parameters models*: The existence of efficient estimators is guaranteed for linear-in-parameter models [51]. The results of ST-segment polynomial models in Section V-B also approve this finding.

Another feature of linear-in-parameter models is that their ML CRLB is independent from the parameter values. Therefore, the CRLB gives a general performance bound (regardless of the parameter value). However, for nonlinear-in-parameter models, the CRLB changes with the model parameters. Therefore, for example, while polynomial fitting over the baseline and the ST-segment have identical properties and CRLB bounds, the CRLB of Gaussian models fitted over the QRS and T-waves depend on both the amplitudes and widths of these waves.

VII. CONCLUSION

ECG parameter estimation performed by human experts and machines and algorithms is “always” model-based (implicitly or explicitly). Therefore, depending on the adopted model and the estimation scheme (LS, ML, or Bayesian), there are theoretical bounds on the achievable accuracy of *any* estimation algorithm. An important implication of this debate is that performance bounds such as the CRLB only depend on

the adopted data-model and estimation scheme, and not the choice of the estimation algorithm itself.

In this research, the CRLB was derived for the most popular data-models used in the ECG literature (polynomial expansions and sum-of-Gaussians). The framework was validated over real and synthetic data for three practical applications: T/R ratio, ST-segment and QT-interval estimation, using state-of-the-art estimators in each context. The results of this study can guide researchers towards the selection of data-models, sampling frequency, modeling segment length, and the number of beats/channels required for average ECG beat extraction.

The work can be extended from various aspects. From the modeling perspective, ECG models such as Legendre polynomials and Splines can be used [10], [31], which have interesting theoretical and practical properties. The derivation of the CRLB for alternative ECG models and their analytical/numeric comparison with the hereby presented results would be highly insightful.

Model priors’ assessment is another direction for future studies. Specifically, the impact of modeling errors (in the data-model, priors or posteriors) is of significant importance. For instance, depending on the parameter of interest and the measurement noise type, distributions such as Rayleigh, Poisson, Gamma, Gaussian mixtures, etc., can be used for specific scenarios. The impact of accurate vs approximate prior/posterior assumptions on the theoretical bounds of ML and Bayesian frameworks can be studied in this context [21].

Finally, from the estimation perspective, the development of estimation algorithms, which reach the theoretical CRLB bounds would be of great practical importance.

APPENDIX

ESTIMATION SCHEMES AND PERFORMANCE BOUNDS

The influential factors in model-based estimation performance are: A) a (parametric) data-model, B) stochastic assumptions on the model parameters (priors), C) stochastic assumptions on the observation noise (posteriors), and D) an estimation algorithm. The basic estimation theoretical schemes used within the text are reviewed for reference.

A. Estimation performance bounds

1) *Least squares*: When only a data-model is available, without priors and posteriors on the stochastic model parameters and observation noise, the LS family (linear, nonlinear, weighted, constrained, recursive, etc.) is the most common estimation scheme. Following the notations defined in Section II, for the additive noise model in (2), the LS estimate of the parameter vector θ is

$$\hat{\theta}_{\text{LS}} = \arg \min_{\theta} \|\mathbf{x} - \tilde{\mathbf{x}}(\theta)\|^2. \quad (24)$$

A modification of the standard LS scheme is when the noise is zero-mean with a presumed covariance matrix $\Sigma_e = \mathbb{E}\{\mathbf{e}\mathbf{e}^T\}$. In this case, *weighted least squares* (WLS) can be used:

$$\hat{\theta}_{\text{WLS}} = \arg \min_{\theta} \|\mathbf{x} - \tilde{\mathbf{x}}(\theta)\|_{\Sigma_e^{-1}}^2 \quad (25)$$

where $\|\mathbf{A}\|_{\Sigma_e^{-1}}^2$ denotes $\mathbf{A}^T \Sigma_e^{-1} \mathbf{A}$. Note that Σ_e is generally non-diagonal (corresponding to colored noise). The intuition behind (25) is to whiten the additive noise and to weight the noisy observations with the inverse of their noise variances (giving smaller weights to the noisier samples).

2) *Maximum likelihood*: ML seeks

$$\hat{\theta}_{\text{ML}} = \arg \max_{\theta} f(\mathbf{x} | \theta). \quad (26)$$

and is applicable when in addition to the data-model, the observation noise distribution is also presumed, without having the model parameters' prior distribution, or when the model parameters are deterministic.

The CRLB can be used to find a lower bound on the minimum mean square error (MMSE) estimate of the parameter vector θ . Accordingly, the covariance matrix of $\hat{\theta}(\mathbf{x})$, an arbitrary *unbiased estimator* of the parameter vector (i.e. $\mathbb{E}_{\mathbf{x}}\{\hat{\theta}(\mathbf{x})\} = \theta$), satisfies

$$\mathbb{E}_{\mathbf{x}}\{[\theta - \hat{\theta}(\mathbf{x})][\theta - \hat{\theta}(\mathbf{x})]^T\} \succeq \mathbf{C}_{\text{ML}} = \mathcal{I}_{\text{ML}}^{-1} \quad (27)$$

where $\mathcal{I}_{\text{ML}}$ is the Fisher Information matrix [14]:

$$\mathcal{I}_{\text{ML}}(\theta) = -\mathbb{E}_{\mathbf{x}}\{\nabla_{\theta}^2 \ln f(\mathbf{x} | \theta)\}, \quad (28)$$

∇_{θ}^2 denotes the Hessian matrix operator, and $\mathbf{A} \succeq \mathbf{B}$ denotes $(\mathbf{A} - \mathbf{B})$ being a non-negative definite matrix. An estimator that reaches the CRLB is an *efficient estimator*.

3) *Bayesian scheme*: Bayesian estimation is the most complete estimation scheme in the reviewed trilogy, as it uses the distribution of both the model parameters and the observation noise (whenever available), to minimize an explicit cost function. If $L(\cdot)$ is a symmetric non-decreasing function denoting the cost of estimation error as a function of $\|\theta - \hat{\theta}\|$, a Bayesian estimator seeks

$$\hat{\theta}_{\text{BYS}} = \arg \min_{\hat{\theta}} \mathbb{E}_{\mathbf{x}, \theta}\{L(\|\theta - \hat{\theta}(\mathbf{x})\|)\}. \quad (29)$$

In a Bayesian estimation scheme, the CRLB is

$$\mathbb{E}_{\mathbf{x}, \theta}\{[\theta - \hat{\theta}(\mathbf{x})][\theta - \hat{\theta}(\mathbf{x})]^T\} \succeq \mathbf{C}_{\text{Bys}} = \mathcal{I}_{\text{Bys}}^{-1} \quad (30)$$

where $\mathcal{I}_{\text{Bys}} = -\mathbb{E}_{\mathbf{x}, \theta}\{\nabla_{\theta}^2 \ln f(\mathbf{x}, \theta)\}$ is the *Bayesian Fisher Information* matrix and $f(\mathbf{x}, \theta)$ denotes the joint probability density function of observations and parameters [52]. Replacing the joint distribution with the conditional form results in

$$\mathcal{I}_{\text{Bys}} = -\mathbb{E}_{\theta}\{\mathbb{E}_{\mathbf{x}}\{\nabla_{\theta}^2 \ln f(\mathbf{x} | \theta)\}\} - \mathbb{E}_{\theta}\{\nabla_{\theta}^2 \ln f(\theta)\}. \quad (31)$$

Defining the *prior Fisher Information* as $\mathcal{I}_{\text{Prior}} = -\mathbb{E}_{\theta}\{\nabla_{\theta}^2 \ln f(\theta)\}$, using (28) the Bayesian Fisher Information is [52, p. 84]:

$$\mathcal{I}_{\text{Bys}} = \mathbb{E}_{\theta}\{\mathcal{I}_{\text{ML}}\} + \mathcal{I}_{\text{Prior}}. \quad (32)$$

which shows the contribution of priors (whenever available) in reducing the CRLB, as compared with the ML framework.

B. Estimators for Gaussian noise and model parameters

The CRLB only places an upper bound on the estimation performance, but does not generally guide us towards an efficient estimator, for different models, noise and parameter distributions. Following Section II-A, we review estimation schemes based on Gaussian noise and model parameter priors.

1) *Maximum likelihood estimation*: When the measurement noise is *explicitly* assumed to be Gaussian distributed $\mathbf{e} \sim \mathcal{N}(\mathbf{0}, \Sigma_e)$, the WLS scheme in (25) is also the ML estimator [53], [54]. In this case, the gradient of the log-likelihood function, as required for calculating the CRLB from (27) is

$$\nabla_{\theta} \ln f(\mathbf{x} | \theta) = -\frac{\partial \tilde{\mathbf{x}}(\theta)^T}{\partial \theta} \Sigma_e^{-1} (\mathbf{x} - \tilde{\mathbf{x}}(\theta)) \quad (33)$$

where $\frac{\partial \tilde{\mathbf{x}}(\theta)}{\partial \theta} = \left[\frac{\partial \tilde{x}_1(\theta)}{\partial \theta}, \dots, \frac{\partial \tilde{x}_N(\theta)}{\partial \theta} \right]^T$, and the Fisher Information matrix is obtained as follows (cf. [52, P. 83]):

$$\mathcal{I}_{\text{ML}}(\theta) = \frac{\partial \tilde{\mathbf{x}}(\theta)^T}{\partial \theta} \Sigma_e^{-1} \frac{\partial \tilde{\mathbf{x}}(\theta)}{\partial \theta} \quad (34)$$

which has an interpretation in terms of the *signal-to-noise matrix* of the noisy data-model (1) (cf. [55] for the definition of an SNR matrix). For the special case of *linear-in-parameter* models $\tilde{\mathbf{x}}(\theta) = \mathbf{H}\theta$ with zero-mean Gaussian noise, we obtain

$$\hat{\theta}_{\text{ML}} = \arg \min_{\theta} \|\mathbf{x} - \mathbf{H}\theta\|_{\Sigma_e^{-1}}^2 = (\mathbf{H}^T \Sigma_e^{-1} \mathbf{H})^{-1} \mathbf{H}^T \Sigma_e^{-1} \mathbf{x} \quad (35)$$

and the Fisher Information is $\mathcal{I}_{\text{ML}} = \mathbf{H}^T \Sigma_e^{-1} \mathbf{H}$, where $\mathbf{H} = [\mathbf{h}_1, \dots, \mathbf{h}_P] \in \mathbb{R}^{N \times P}$ is the matrix of P bases vectors used for modeling the SoI $\mathbf{x}$. For *nonlinear in parameter* models with additive Gaussian noise, the ML estimate reduces to a nonlinear LS problem, and the general nonlinear case with non-gaussian noise is solved by iterative methods such as *Expectation-Maximization (EM)*, which converge to the ML solution under some general conditions [56].

2) *Bayesian estimation*: In addition to the data-model and noise distribution, a full Bayesian framework requires the parameter distribution and an optimization criterion (i.e. a cost function to minimize). As a popular case, if the parameter vector is normally distributed, i.e. $\theta \sim \mathcal{N}(\mu_\theta, \Sigma_\theta)$, the optimal estimator, which minimizes the cost of error (29) satisfies

$$\hat{\theta}_{\text{BYS}} = \arg \min_{\theta} \{ \|x - \tilde{x}(\theta)\|_{\Sigma_e^{-1}}^2 + \|\theta - \mu_\theta\|_{\Sigma_\theta^{-1}}^2 \}. \quad (36)$$

which is in the form of generalized *Tikhonov regularization* [57]. Under the Gaussian distribution assumption, the *maximum a posteriori* (MAP), the *minimum mean square error* (MMSE) and several other well-known estimation schemes result in the same estimator [52, Sec. 2.4], making MAP and MMSE estimation schemes identical.

For linear-in-parameters models of the form $\tilde{x}(\theta) = \mathbf{H}\theta$, (36) results in a closed form solution [58]:

$$\begin{aligned} \hat{\theta}_{\text{BYS}} &= (\mathbf{H}^T \Sigma_e^{-1} \mathbf{H} + \Sigma_\theta^{-1})^{-1} (\mathbf{H}^T \Sigma_e^{-1} x + \Sigma_\theta^{-1} \mu_\theta) \\ &= \mu_\theta + (\mathbf{H}^T \Sigma_e^{-1} \mathbf{H} + \Sigma_\theta^{-1})^{-1} \mathbf{H}^T \Sigma_e^{-1} (x - \mathbf{H} \mu_\theta). \end{aligned} \quad (37)$$

However, for the nonlinear models such as sum-of-Gaussians, the solution is practically obtained by using nonlinear LS algorithms. For this, one first defines the vector:

$$y(\theta) \triangleq \begin{bmatrix} (x - \tilde{x}(\theta)) \Sigma_e^{-1/2} \\ (\theta - \mu_\theta) \Sigma_\theta^{-1/2} \end{bmatrix}. \quad (38)$$

and (36) equates $\hat{\theta}_{\text{BYS}} = \arg \min_{\theta} \{y(\theta)^T y(\theta)\}$, which can be solved by nonlinear LS algorithms such as *trust-region-reflective* [59], or *Levenberg-Marquardt* [60]. In Section V, all nonlinear schemes (LS, ML and Bayesian) were implemented by the trust-region-reflective algorithm.

REFERENCES

- [1] J. Lázaro, N. Reljin, M.-B. Hossain *et al.*, “Wearable armband device for daily life electrocardiogram monitoring,” *IEEE Transactions on Biomedical Engineering*, vol. 67, no. 12, pp. 3464–3473, 2020.
- [2] D. Hernando, A. Hernando, J. A. Casajús *et al.*, “Methodological framework for heart rate variability analysis during exercise: application to running and cycling stress testing,” *Medical & Biological Engineering & Computing*, vol. 56, no. 5, pp. 781–794, Sep. 2017. [Online]. Available: <https://doi.org/10.1007/s11517-017-1724-9>
- [3] R. Sameni, *Noninvasive Fetal Electrocardiography: Models, Technologies, and Algorithms*. Cham: Springer International Publishing, 2021, pp. 99–146. [Online]. Available: https://doi.org/10.1007/978-3-030-54403-4_5
- [4] D. G. Strauss and D. D. Schocken, *Marriott’s practical electrocardiography*, 13th ed. Philadelphia: Wolters Kluwer, 2021.
- [5] A. de Luna, *Clinical Electrocardiography: A Textbook*. Wiley, 1998.
- [6] P. Laguna, R. Jane, and P. Caminal, “Automatic detection of wave boundaries in multilead ECG signals: validation with the CSE database,” *Comput. Biomed. Res.*, vol. 27, no. 1, pp. 45–60, Feb 1994.
- [7] A. Y. Hannun, P. Rajpurkar, M. Haghpanahi *et al.*, “Cardiologist-level arrhythmia detection and classification in ambulatory electrocardiograms using a deep neural network,” *Nature Medicine*, vol. 25, no. 1, pp. 65–69, Jan. 2019. [Online]. Available: <https://doi.org/10.1038/s41591-018-0268-3>
- [8] L. Sornmo, P. O. Borjesson, M.-E. Nygard, and O. Pahlm, “A method for evaluation of QRS shape features using a mathematical model for the ECG,” *IEEE Transactions on Biomedical Engineering*, vol. BME-28, no. 10, pp. 713–717, Oct. 1981. [Online]. Available: <https://doi.org/10.1109/tbme.1981.324666>
- [9] P. Laguna, R. Jané, S. Olmos *et al.*, “Adaptive estimation of QRS complex by the hermite model for classification and ectopic beat detection,” *Med. Biol. Eng. Comput.*, vol. 34, no. 1, pp. 58–68, 1996.
- [10] E. K. Roonizi and R. Sameni, “Morphological modeling of cardiac signals based on signal decomposition,” *Computers in Biology and Medicine*, vol. 43, no. 10, pp. 1453–1461, October 2013. [Online]. Available: <http://dx.doi.org/10.1016/j.combiomed.2013.06.017>
- [11] P. E. McSharry, G. D. Clifford, L. Tarassenko, and L. A. Smith, “A Dynamic Model for Generating Synthetic Electrocardiogram Signals,” *Biomedical Engineering, IEEE Transactions on*, vol. 50, pp. 289–294, mar 2003.
- [12] R. Sameni, G. D. Clifford, C. Jutten, and M. B. Shamsollahi, “Multichannel ECG and Noise Modeling: Application to Maternal and Fetal ECG Signals,” *EURASIP Journal on Advances in Signal Processing*, vol. 2007, pp. Article ID 43407, 14 pages, 2007. [Online]. Available: <https://doi.org/10.1155/2007/43407>
- [13] M. Akhbari, M. B. Shamsollahi, C. Jutten *et al.*, “ECG denoising and fiducial point extraction using an extended Kalman filtering framework with linear and nonlinear phase observations,” *Physiological Measurement*, vol. 37, no. 2, pp. 203–226, Jan. 2016. [Online]. Available: <https://doi.org/10.1088/0967-3334/37/2/203>
- [14] S. M. Kay, *Fundamentals of Statistical Signal Processing: Estimation Theory*. Upper Saddle River, NJ, USA: Prentice-Hall, Inc., 1993.
- [15] G. Clifford, A. H. Shoen, P. E. McSharry, and B. Janz, “Model-based filtering, compression and classification of the ECG,” *International Journal of Bioelectromagnetism*, vol. 7, no. 1, pp. 158–161, 2005. [Online]. Available: <http://www.ijbem.org/volume7/number1/158-161.pdf>
- [16] G. Clifford, F. Azuaje, and P. McSharry, *Advanced methods and tools for ECG data analysis*, ser. Artech House engineering in medicine & biology series. Artech House, 2006.
- [17] C. Bock, P. Kovacs, P. Laguna *et al.*, “Ecg beat representation and delineation by means of variable projection,” *IEEE Transactions on Biomedical Engineering*, pp. 1–1, 2021.
- [18] B. Rivet, M. Niknazar, and C. Jutten, “Nonparametric modelling of ecg: applications to denoising and to single sensor fetal ecg extraction,” in *International Conference on Latent Variable Analysis and Signal Separation*. Springer, 2012, pp. 470–477.
- [19] R. Sameni, M. B. Shamsollahi, C. Jutten, and G. D. Clifford, “A nonlinear bayesian filtering framework for ECG denoising,” *Biomedical Engineering, IEEE Transactions on*, vol. 54, no. 12, pp. 2172–2185, December 2007. [Online]. Available: <https://doi.org/10.1109/TBME.2007.897817>
- [20] T. Zhu, A. E. Johnson, J. Behar, and G. D. Clifford, “Crowd-sourced annotation of ECG signals using contextual information,” *Annals of biomedical engineering*, vol. 42, no. 4, pp. 871–884, 2014.
- [21] S. Fortunati, F. Gini, M. S. Greco, and C. D. Richmond, “Performance Bounds for Parameter Estimation under Misspecified Models: Fundamental Findings and Applications,” *IEEE Signal Processing Magazine*, vol. 34, no. 6, pp. 142–157, 2017.
- [22] P. M. Rautaharju, P. J. MacInnis, J. W. Warren *et al.*, “Methodology of ECG interpretation in the Dalhousie program; NOVACODE ECG classification procedures for clinical trials and population health surveys,” *Methods Inf Med*, vol. 29, no. 4, pp. 362–374, Sep 1990.
- [23] L. G. Herrera-Bendezu and B. G. Denys, “Feature identification of ECG waveforms via orthonormal functions,” in *[1990] Proceedings Computers in Cardiology*, Sep. 1990, pp. 641–644.
- [24] J. Ben-Arie and K. Rao, “Nonorthogonal representation of signals by Gaussians and Gabor functions,” *IEEE Trans. Circuits Syst. II*, vol. 42, no. 6, pp. 402–413, June 1995.
- [25] O. Sayadi, M. Shamsollahi, and G. Clifford, “Robust detection of premature ventricular contractions using a wave-based bayesian framework,” *Biomedical Engineering, IEEE Transactions on*, vol. 57, no. 2, pp. 353–362, feb. 2010.
- [26] P. Kligfield, F. Badilini, I. Denjoy *et al.*, “Comparison of automated interval measurements by widely used algorithms in digital electrocardiographs,” *American Heart Journal*, vol. 200, pp. 1–10, 2018. [Online]. Available: <https://www.sciencedirect.com/science/article/pii/S0002870318300620>
- [27] J. Leski, “Robust weighted averaging [of biomedical signals],” *Biomedical Engineering, IEEE Transactions on*, vol. 49, no. 8, pp. 796–804, 2002.
- [28] M. Reyna, N. Sadr, A. Gu *et al.*, “Will Two Do? Varying Dimensions in Electrocardiography: the PhysioNet - Computing in Cardiology Challenge 2021,” 2021. [Online]. Available: <https://physionet.org/content/challenge-2021/1.02/>
- [29] F. Pelliccia, M. Ciavolella, A. Gaspardone *et al.*, “Idiopathic dilated cardiomyopathy: T/R ratio as an ECG index of ventricular volume and function,” *Cardiologia*, vol. 32, no. 3, pp. 281–286, March 1987.

- [30] *The PTB Diagnostic ECG Database*, Physikalisch-Technische Bundesanstalt (PTB). [Online]. Available: <http://www.physionet.org/physiobank/database/ptbdb/>
- [31] M. Amon and F. Jager, "Electrocardiogram ST-Segment Morphology Delineation Method Using Orthogonal Transformations," *PLOS ONE*, vol. 11, no. 2, pp. 1–18, 02 2016. [Online]. Available: <https://doi.org/10.1371/journal.pone.0148814>
- [32] S. J. Weisner, W. J. Tompkins, and B. M. Tompkins, "A compact, microprocessor-based ECG ST-segment analyzer for the operating room," *IEEE Transactions on Biomedical Engineering*, vol. BME-29, no. 9, pp. 642–649, 1982.
- [33] F. Extramiana, J. Seitz, P. Maison-Blanche *et al.*, "Quantitative assessment of ST segment elevation in Brugada patients," *Heart Rhythm*, vol. 3, no. 10, pp. 1175–1181, Oct 2006.
- [34] F. Badilini, M. Merri, J. Benhorin, and A. J. Moss, "Beat-to-beat quantification and analysis of ST displacement from Holter ECGs: a new approach to ischemia detection," in *Proceedings Computers in Cardiology*, 1992, pp. 179–182.
- [35] A. Mincholé, F. Jager, and P. Laguna, "Discrimination between ischemic and artifactual ST segment events in Holter recordings," *Biomedical Signal Processing and Control*, vol. 5, no. 1, pp. 21 – 31, 2010. [Online]. Available: <http://www.sciencedirect.com/science/article/pii/S1746809409000895>
- [36] K. Watanabe, V. Bhargava, and V. Froelicher, "Computer analysis of the exercise ECG: A review," *Progress in Cardiovascular Diseases*, vol. 22, no. 6, pp. 423 – 446, 1980. [Online]. Available: <http://www.sciencedirect.com/science/article/pii/0033062080900171>
- [37] F. Jager, A. Taddei, G. B. Moody *et al.*, "Long-term ST database: a reference for the development and evaluation of automated ischaemia detectors and for the study of the dynamics of myocardial ischaemia," *Med Biol Eng Comput*, vol. 41, no. 2, pp. 172–182, Mar 2003.
- [38] R. Bousseljot, D. Kreiseler, and A. Schnabel, "Nutzung der EKG-Signaldatenbank CARDIODAT der PTB über das Internet," *Biomedizinische Technik/Biomedical Engineering*, pp. 317–318, Jul. 2009. [Online]. Available: <https://doi.org/10.1515/bmte.1995.40.s1.317>
- [39] R. Sameni, *The Open-Source Electrophysiological Toolbox (OSET)*, version 3.14, 2018. [Online]. Available: <http://www.oset.ir>
- [40] R. Sameni, C. Jutten, and M. B. Shamsollahi, "Multichannel Electrocardiogram Decomposition using Periodic Component Analysis," *Biomedical Engineering, IEEE Transactions on*, vol. 55, no. 8, pp. 1935–1940, Aug 2008. [Online]. Available: <https://doi.org/10.1109/TBME.2008.919714>
- [41] F. A. Afsar, M. S. Riaz, and M. Arif, "A comparison of baseline removal algorithms for electrocardiogram (ECG) based automated diagnosis of coronary heart disease," in *3rd International Conference on Bioinformatics and Biomedical Engineering*. IEEE, Jun. 2009. [Online]. Available: <https://doi.org/10.1109/icbbe.2009.5162156>
- [42] C. Pérez, E. Pueyo, J. P. Martínez *et al.*, "Characterization of impaired ventricular repolarization by quantification of QT delayed response to heart rate changes in stress test," in *2020 Computing in Cardiology*, 2020, pp. 1–4.
- [43] O. Sayadi and M. B. Shamsollahi, "A model-based Bayesian framework for ECG beat segmentation," *Physiol Meas*, vol. 30, no. 3, pp. 335–352, Mar 2009.
- [44] G. Clifford and M. Villarroel, "Model-based determination of QT intervals," in *2006 Computers in Cardiology*. IEEE, 2006, pp. 357–360.
- [45] P. Laguna, R. Mark, A. Goldberg, and G. Moody, "A database for evaluation of algorithms for measurement of QT and other waveform intervals in the ECG," in *Computers in Cardiology 1997*, 1997, pp. 673–676.
- [46] H. Leutheuser, S. Gradl, L. Anneken *et al.*, "Instantaneous P- and T-wave detection: Assessment of three ECG fiducial points detection algorithms," in *2016 IEEE 13th International Conference on Wearable and Implantable Body Sensor Networks (BSN)*, 2016, pp. 329–334.
- [47] J. P. Martinez, R. Almeida, S. Olmos *et al.*, "A wavelet-based ECG delineator: evaluation on standard databases," *IEEE Transactions on Biomedical Engineering*, vol. 51, no. 4, pp. 570–581, 2004.
- [48] N. Spicher and M. Kukuk, "Delineation of electrocardiograms using multiscale parameter estimation," *IEEE Journal of Biomedical and Health Informatics*, vol. 24, no. 8, pp. 2216–2229, 2020.
- [49] J. M. Bote, J. Recas, F. Rincón *et al.*, "A modular low-complexity ecg delineation algorithm for real-time embedded systems," *IEEE Journal of Biomedical and Health Informatics*, vol. 22, no. 2, pp. 429–441, 2018.
- [50] L. Y. D. Marco and L. Chiari, "A wavelet-based ECG delineation algorithm for 32-bit integer online processing," *BioMedical Engineering OnLine*, vol. 10, no. 1, p. 23, 2011. [Online]. Available: <https://doi.org/10.1186/1475-925x-10-23>
- [51] A. Host-Madsen, "On the existence of efficient estimators," *IEEE Transactions on Signal Processing*, vol. 48, no. 11, pp. 3028–3031, Nov 2000.
- [52] H. van Trees, *Detection, Estimation, and Modulation Theory. Part I*. John Wiley & Sons, 2001.
- [53] S. Gezici, I. Guvenc, and Z. Sahinoglu, "On the performance of linear least-squares estimation in wireless positioning systems," in *2008 IEEE International Conference on Communications*, 2008, pp. 4203–4208.
- [54] P. Handel, "Cramér-rao bounds and non-linear least squares for a seven parameter dual channel sinewave model," in *2007 IEEE Instrumentation Measurement Technology Conference IMTC 2007*, 2007, pp. 1–6.
- [55] G. Reeves, H. D. Pfister, and A. Dytso, "Mutual Information as a Function of Matrix SNR for Linear Gaussian Channels," in *2018 IEEE International Symposium on Information Theory (ISIT)*. IEEE, jun 2018. [Online]. Available: <https://dx.doi.org/10.1109/isit.2018.8437326>
- [56] S. Balakrishnan, M. J. Wainwright, and B. Yu, "Statistical guarantees for the EM algorithm: From population to sample-based analysis," *Ann. Statist.*, vol. 45, no. 1, pp. 77–120, 02 2017. [Online]. Available: <https://doi.org/10.1214/16-AOS1435>
- [57] N. G. Polson and V. Sokolov, "Bayesian regularization: From tikhonov to horseshoe," *WIREs Computational Statistics*, vol. 11, no. 4, p. e1463, 2019. [Online]. Available: <https://onlinelibrary.wiley.com/doi/abs/10.1002/wics.1463>
- [58] C. R. Vogel, *Computational Methods for Inverse Problems*. Society for Industrial and Applied Mathematics, Jan. 2002. [Online]. Available: <https://doi.org/10.1137/1.9780898717570>
- [59] T. F. Coleman and Y. Li, "An interior trust region approach for nonlinear minimization subject to bounds," *SIAM Journal on Optimization*, vol. 6, no. 2, pp. 418–445, May 1996. [Online]. Available: <https://doi.org/10.1137/0806023>
- [60] J. J. Moré, "The levenberg-marquardt algorithm: Implementation and theory," in *Lecture Notes in Mathematics*. Springer Berlin Heidelberg, 1978, pp. 105–116. [Online]. Available: <https://doi.org/10.1007/bfb0067700>