

# Estimation of Shape Constrained Functions in Dynamical Systems and Its Application to Gene Networks

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**Abstract**—Inspired by estimation and identification of biological and engineering systems subject to constraints, this paper addresses nonparametric estimation of monotone functions contained in a class of dynamical systems. A two-stage estimation procedure is proposed. At the first stage, partial state estimation is performed via trend filtering techniques. At the second stage, a penalized spline (or P-spline for short) estimator is used to estimate monotone functions. The highlight of the paper is asymptotic analysis of the monotone P-spline estimator formulated as a constrained optimization problem. The uniform Lipschitz property is established for optimal spline coefficients. By approximating the estimator by a solution of a differential equation with a constrained right-hand side, the paper develops asymptotic normality at interior points and establishes convergence rates. The proposed estimator is applied to estimation of a monotone regulatory function in a gene regulatory network.

## I. INTRODUCTION

Many biological, economic, and engineering systems are subject to constraints. Dynamical systems with constrained components can be formulated as piecewise smooth systems, which belong to the general framework of switching and hybrid systems. Estimation and identification of switching and hybrid systems has received fast growing interest in recent years, driven by important applications in engineering, robotics, and systems biology. For example, several effective estimation and identification algorithms have been proposed for piecewise affine systems [4], [6], [12].

Motivated by estimation of regulatory functions in gene regulatory networks, this paper studies nonparametric estimation of shape constrained functions, specifically monotone functions, in dynamical systems. A two-stage procedure is proposed to estimate such monotone functions. At the first stage, partial state estimation is performed by exploiting trend filtering methods, e.g. Hodrick-Prescott filtering or  $\ell_1$  trend filtering [7]. At the second stage, a penalized monotone spline regression estimator (or simply  $P$ -spline estimator) recently developed in [14] is considered. A monotone function is approximated by a spline of an arbitrary degree, and the estimator is defined by an optimal solution of a quadratic programming subject to the first-order difference penalty and the monotone constraint. Focused issues of the  $P$ -spline estimator include asymptotic behaviors, for instance, the asymptotic distribution of the estimator and the related convergence rates with respect to the number of measurement

points. To address these issues, a critical uniform Lipschitz property is developed for the optimal spline coefficients and yields consistency and stochastic boundedness of the estimator. The optimality conditions show that the estimator can be approximated by an ODE with a constrained right-hand side. Using this ODE, asymptotic normality and convergence rates are established. Compared with the existing methods for estimation and identification of constrained systems, the present paper treats nonparametric estimation of monotone functions and studies asymptotic behaviors by employing complementarity theory [2] and asymptotic statistics.

The rest of the paper is organized as follows. In Section II, we introduce the dynamical model and present a motivating example of gene regulatory networks. Section III addresses partial state estimation and Section IV discusses monotone estimation and its asymptotic analysis. A numerical example from gene regulatory networks illustrates the proposed estimator in Section V. Finally, conclusions are made in Section VI. Due to space limitation, the proofs of theoretical results in this paper are omitted and can be found in cited references, e.g. [14].

## II. MODEL AND EXAMPLE

Consider the following discrete-time dynamic system:

$$x(k+1) = Ax(k) + bz(k) + \varepsilon_d(k) \quad (1a)$$

$$z(k) = f(h^T x(k)) \quad (1b)$$

$$y(k) = c^T x(k) + \varepsilon_y(k) \quad (1c)$$

where  $k \in \mathbb{Z}_+$ ,  $x \in \mathbb{R}^n$  is the system state,  $A \in \mathbb{R}^{n \times n}$  is the known state transition matrix,  $b, h, c \in \mathbb{R}^n$  are the given nonzero vectors,  $z$  denotes the feedback,  $y$  is the measurement output,  $f: \mathcal{I} \rightarrow \mathbb{R}$  is an unknown monotone function defined on a given compact interval  $\mathcal{I} \subset \mathbb{R}$ , and  $\varepsilon_d \in \mathbb{R}^n$  and  $\varepsilon_y \in \mathbb{R}$  are the dynamic and measurement noises respectively. The goal of this paper is to use the measurement  $y$ , together with other measurements, to estimate the monotone function  $f$  and carry out asymptotic analysis.

The above model represents a wide range of biological and engineering systems with unknown monotone components that need to be estimated. The following example shows an interesting application in gene regulatory networks [3], [4].

**Example 1** The expression of genes in an organism is controlled by regulatory systems via a complex network of interactions between DNA, RNA, proteins and small molecules [1], [3]. A thorough understanding of dynamic behaviors of the regulatory networks is essential to biomedical science and

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engineering [5]. To achieve this goal, various mathematical models have been developed, one of which is the following ODE system (without noise) [3]:

$$\dot{x} = Ex + dr(x_n) \quad (2)$$

where the state vector  $x = (x_1, \dots, x_n)^T \in \mathbb{R}_+^n$ ,  $x_i \geq 0$  denotes the concentration of the  $i$ th protein, and the  $n \times n$  matrix  $E$  and the  $n$ -vector  $d$  are respectively given by

$$E = \begin{bmatrix} -\gamma_1 & & & & & \\ k_2 & -\gamma_2 & & & & \\ & \ddots & \ddots & & & \\ & & & k_{n-1} & -\gamma_{n-1} & \\ & & & & k_n & -\gamma_n \end{bmatrix}, \quad d = \begin{bmatrix} 1 \\ 0 \\ \vdots \\ 0 \\ 0 \end{bmatrix},$$

where  $k_1, \dots, k_n$  are positive production constants, and  $\gamma_1, \dots, \gamma_n$  are positive degradation constants. Here  $r(x_n) \equiv k_1[1 - h^+(x_n, \theta)]$  is an unknown switching regulation function, where  $\theta > 0$  is the threshold of switching, and plays a crucial role in the gene network dynamics. It is known that  $h^+(\cdot, \theta)$  is an increasing function [3]. However, the closed form expression of  $h^+$  and its threshold value  $\theta$  are usually unavailable and may vary from one network to another. Certain approximations of  $h^+$  are proposed in the literature. Figure 1 shows the graph of a piecewise linear formulation of  $h^+(\cdot, \theta)$ ; other formulations, including the Heaviside function, can be found in [3]. To obtain a discrete-time model for (2), let  $\tau > 0$  be the time step and we have

$$x(k+1) = Ax(k) + bf(h^T x(k)), \quad y(k) = c^T x(k),$$

where  $A \equiv e^{E\tau}$ ,  $b \equiv \int_0^\tau e^{E(\tau-s)} ds$ ,  $f(\cdot) \equiv r(\cdot)$  and  $c = h = (0, \dots, 0, 1)^T$ . By including the dynamic and measurement noise, we obtain the discrete-time model (1).

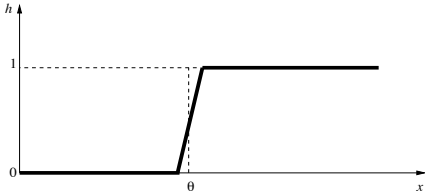


Fig. 1. Piecewise linear approximation of the monotone function  $h^+$

**Remark 2** A more complex multi-output dynamic model similar to (1) can be considered. Moreover the parameters in the system (1) may be assumed to be unknown and can be identified along with monotone estimation. We refer the interested reader to the monograph [9] for extensive discussions on system identification. On the other hand, since our primary focus is estimation of the monotone component  $f$ , we are content with the relatively simpler model (1) and the assumption of the known parameters to avoid distraction from the main theme of this paper. The general situation will be addressed in the future.

### III. PARTIAL STATE ESTIMATION

To estimate the monotone function  $f$ , one needs the information about  $h^T x(k)$  and  $z(k)$  that can be attained via partial state estimation. We shall consider two cases as follows: (i) the measurement  $z(k)$  is available; (ii) otherwise.

#### A. Available $z(k)$

The measurement  $z(k)$  is generally contaminated by additional measurement noise. In view of this, we rewrite equation (1) by including the noise  $\varepsilon_z(k) \in \mathbb{R}$  as

$$x(k+1) = Ax(k) + bf(h^T x(k)) + \varepsilon_d(k) \quad (3a)$$

$$z(k) = f(h^T x(k)) + \varepsilon_z(k) \quad (3b)$$

$$y(k) = c^T x(k) + \varepsilon_y(k) \quad (3c)$$

Since  $z(k)$  is available, we only need to construct  $h^T x(k)$ . To reach this goal, the following assumption is made:

**Assumption 1:**  $(c^T, A)$  is an observable pair.

Under this assumption, the  $n \times n$  matrix

$$\mathbf{G} \equiv [c \quad A^T c \quad \dots \quad (A^{n-1})^T c]^T$$

is invertible. Defining three  $n$ -vectors  $\mathbf{y}(k) \equiv (y(k), y(k+1), \dots, y(k+n-1))^T$ ,

$$\mathbf{w}(k) \equiv \left( 0, c^T b z(k), \sum_{i=0}^1 c^T A^i b z(k+1-i), \dots, \sum_{i=0}^{n-2} c^T A^i b z(k+n-2-i) \right)^T,$$

and

$$\mathbf{e}(k) \equiv \begin{bmatrix} \varepsilon_y(k) \\ \varepsilon_y(k+1) + c^T q(k) \\ \varepsilon_y(k+2) + \sum_{i=0}^1 c^T A^i q(k+1-i) \\ \vdots \\ \varepsilon_y(k+n-1) + \sum_{i=0}^{n-2} c^T A^i q(k+n-2-i) \end{bmatrix},$$

where  $q(k) \equiv \varepsilon_d(k) - b\varepsilon_z(k)$ , it is easy to verify that

$$\mathbf{y}(k) = \mathbf{G} x(k) + \mathbf{w}(k) + \mathbf{e}(k)$$

Since  $\mathbf{y}(k)$  and  $\mathbf{w}(k)$  are available, so is  $\tilde{\mathbf{y}}(k) \equiv h^T \mathbf{G}^{-1} (\mathbf{y}(k) - \mathbf{w}(k))$  and we obtain a time series

$$\tilde{\mathbf{y}}(k) = \tilde{\mathbf{x}}(k) + \tilde{\mathbf{e}}(k),$$

where  $\tilde{\mathbf{x}}(k) \equiv h^T x(k)$  and  $\tilde{\mathbf{e}}(k) \equiv h^T \mathbf{G}^{-1} \mathbf{e}(k)$  represents the noise. We assume that  $\varepsilon_d(k)$  is an independent and identically-distributed (i.i.d.) Gaussian random vector with mean zero and covariance matrix  $\sigma_d^2 I$ , and  $\varepsilon_y(k), \varepsilon_z(k)$  are i.i.d. Gaussian random variables with mean zero and variance  $\sigma_y^2, \sigma_z^2$  respectively. Furthermore,  $\varepsilon_d(k), \varepsilon_z(k)$  and  $\varepsilon_y(k)$  are assumed to be independent of each other. Hence,  $\tilde{\mathbf{e}}(k)$  is normally distributed with mean zero. It is assumed that  $\sigma_d^2$  is much smaller than  $\sigma_z^2$  and  $\sigma_y^2$ . Therefore the underlying trend  $\tilde{\mathbf{x}}(k)$  has slow and small variations while  $\tilde{\mathbf{e}}(k)$  is a larger and more rapidly varying random component.

To estimate  $\tilde{\mathbf{x}}(k)$ , we consider either of the following trend filtering methods [7]:

- (1) Hodrick-Prescott filtering: this filtering is used to find the unique solution  $\{\tilde{\mathbf{x}}^*(k)\}$  of the penalized optimization problem  $\min \frac{1}{2} \|\tilde{\mathbf{y}} - \tilde{\mathbf{x}}^*\|_2^2 + \lambda \|\tilde{D}\tilde{\mathbf{x}}^*\|_2^2$ ;
- (2)  $\ell_1$  trend filtering: similar to (1), this filtering is used to find the unique solution  $\{\tilde{\mathbf{x}}^*(k)\}$  of the optimization problem  $\min \frac{1}{2} \|\tilde{\mathbf{y}} - \tilde{\mathbf{x}}^*\|_2^2 + \lambda \|\tilde{D}\tilde{\mathbf{x}}^*\|_1$ ,

where  $\lambda > 0$  is the penalty parameter,  $\tilde{\mathbf{y}} \equiv (\tilde{y}(1), \dots, \tilde{y}(N))^T$ ,  $\tilde{\mathbf{x}}^* \equiv (\tilde{x}^*(1), \dots, \tilde{x}^*(N))^T$ , and the  $(N-2) \times N$  second-order difference matrix is

$$\tilde{D} = \begin{bmatrix} 1 & -2 & 1 & & & & \\ & 1 & -2 & 1 & & & \\ & & \ddots & \ddots & \ddots & & \\ & & & 1 & -2 & 1 & \\ & & & & 1 & -2 & 1 \end{bmatrix}.$$

The analytical and numerical properties of the Hodrick-Prescott filtering and  $\ell_1$  trend filtering can be found in [7].

### B. Unavailable $z(k)$

If  $z(k)$  is not available, then more output measurements are needed to estimate  $h^T x(k)$  and  $z(k)$ . For this end, we make the following assumption in addition to Assumption 1:

**Assumption 2:** There exist an index subset  $\alpha \subseteq \{1, \dots, n\}$  and a vector  $c_\alpha \in \mathbb{R}^{|\alpha|}$ , where  $|\alpha|$  is the cardinality of  $\alpha$  such that (i)  $c_\alpha^T$  is a left eigenvector of  $A_{\alpha\alpha}$  associated with a real eigenvalue  $\lambda_\alpha$  of  $A_{\alpha\alpha}$ , i.e.,  $c_\alpha^T A_{\alpha\alpha} = \lambda_\alpha c_\alpha^T$ , where  $A_{\alpha\alpha}$  denotes the submatrix of  $A$  with rows indexed by  $\alpha$  and columns indexed by  $\alpha$ ; (ii)  $c_\alpha^T A_{\alpha j} = 0$  for any  $j \in \{1, \dots, n\} \setminus \alpha$ ; and (iii)  $c_\alpha^T b_\alpha \neq 0$ . Besides the measurement  $v(k) \equiv c_\alpha^T x_\alpha(k)$  is available.

By adding the noise  $\varepsilon_v(k) \in \mathbb{R}$  to the measurement  $v$ , equation (1) becomes

$$x(k+1) = Ax(k) + bf(h^T x(k)) + \varepsilon_d(k) \quad (4a)$$

$$y(k) = c^T x(k) + \varepsilon_y(k) \quad (4b)$$

$$v(k) = c_\alpha^T x_\alpha(k) + \varepsilon_v(k) \quad (4c)$$

It follows from Assumption 2 that

$$c_\alpha^T x_\alpha(k+1) = c_\alpha^T A_{\alpha\alpha} x_\alpha(k) + c_\alpha^T b_\alpha f(h^T x(k)) + c_\alpha^T (\varepsilon_d)_\alpha(k)$$

Letting  $\nu \equiv 1/(c_\alpha^T b_\alpha)$ , we have

$$f(h^T x(k)) = \nu \left[ v(k+1) - \lambda_\alpha v(k) - c_\alpha^T (\varepsilon_d)_\alpha(k) - \varepsilon_v(k+1) + \lambda_\alpha \varepsilon_v(k) \right]$$

Define  $z(k) \equiv \nu[v(k+1) - \lambda_\alpha v(k)]$ . Hence  $z(k) = f(h^T x(k)) + \varepsilon_z(k)$ , where  $\varepsilon_z(k) = \nu[c_\alpha^T (\varepsilon_d)_\alpha(k) + \varepsilon_v(k+1) - \lambda_\alpha \varepsilon_v(k)]$ . Following the similar development in the last section, we obtain an estimation of  $h^T x(k)$ , namely,  $\tilde{\mathbf{x}}^*$ , by employing either Hodrick-Prescott filtering or  $\ell_1$  trend filtering under similar assumptions.

## IV. ESTIMATION OF THE MONOTONE FUNCTION $f$

In this section, we estimate the monotone function  $f : \mathcal{I} \rightarrow \mathbb{R}$  on a given interval  $\mathcal{I}$  using  $\tilde{\mathbf{x}}^*$  (i.e. the estimation of  $\{h^T x(k)\}$ ) obtained before. Without loss of generality, consider an increasing  $f$ , i.e.,  $f(s_1) \leq f(s_2)$  once  $s_1 \leq s_2$ , and that  $\mathcal{I} = [0, 1]$ . The following assumption is imposed in order to perform this estimation:

**Assumption 3:**  $\{\tilde{x}^*(k)\} \in [0, 1], \forall k$  and  $\{\tilde{x}^*(k)\}_{k=1}^\ell$  is dense on  $[0, 1]$  as  $\ell \rightarrow \infty$ .

Loosely speaking, this condition assumes persistent excitations of the system in consideration.

We sort the elements of the estimation  $\tilde{\mathbf{x}}^*$  to obtain an increasing vector  $\bar{\mathbf{x}} \equiv \{\bar{x}_k\}$  on  $[0, 1]$ , i.e.,  $0 \leq \bar{x}_i \leq \bar{x}_j \leq 1$  whenever  $i \leq j$ , and let  $\bar{\mathbf{y}} \equiv \{\bar{y}_k\}$  denote the vector formed by the corresponding elements in  $\{z(k)\}$ . For notational simplicity (but somewhat notation abusing), we drop the bars on both  $\bar{x}_i$  and  $\bar{y}_j$  and let  $n \equiv N$ . This gives rise to the monotone regression model:

$$y_i = f(x_i) + \sigma \varepsilon_i, \quad i = 1, \dots, n, \quad (5)$$

where  $x_i$ 's are called the design points,  $\sigma$  is the noise level, and  $\varepsilon_i$ 's are independent standard normal variables. Note that the designed points are not necessarily equally spaced on  $[0, 1]$ . However, the unequally spaced problem can be converted into a relevant equally spaced one and, thus, treated as one thereafter [8], [15]. Hence we focus on the equally spaced case only. To introduce the  $P$ -spline estimator, let  $\{B_k^{[p]} : k = 1, \dots, K_n + p\}$  be the  $p$ th degree B-spline basis with knots  $\kappa_i = i/K_n, i = 0, 1, \dots, K_n$  and  $p \geq 0$ . The value of  $K_n$  depends on  $n$  as discussed below and  $n/K_n$  is assumed to be an integer. Denote  $y \equiv (y_1, \dots, y_n)^T$  and the polyhedral cone  $\mathcal{C} \equiv \{b \in \mathbb{R}^{K_n+p} : b_1 \leq b_2 \leq \dots \leq b_{K_n+p}\}$ . The following quadratic program yields the optimal spline coefficients  $\hat{b} \equiv \{\hat{b}_k, k = 1, \dots, K_n + p\}$ :

$$\hat{b} = \arg \min_{b \in \mathcal{C}} \sum_{i=1}^n [y_i - \sum_{k=1}^{K_n+p} b_k B_k^{[p]}(x_i)]^2 + \lambda^* \sum_{k=2}^{K_n+p} [\Delta(b_k)]^2$$

where  $\lambda^* > 0$  and  $\Delta$  is the backward difference operator, i.e.,  $\Delta b_k \equiv b_k - b_{k-1}$ . The monotone  $P$ -spline estimator is given by

$$\hat{f}^{[p]}(x) = \sum_{k=1}^{K_n+p} \hat{b}_k B_k^{[p]}(x). \quad (6)$$

It is worth mentioning that the above constrained quadratic program can be solved using efficient numerical convex optimization techniques.

### A. Optimality Conditions and Uniform Lipschitz Property

The underlying optimization problem can be put in the following matrix form

$$\hat{b} = \arg \min_{b \in \mathcal{C}} \frac{1}{2} b^T (\Gamma_n + \lambda D^T D) b - b^T \bar{y}, \quad (7)$$

where the  $(K_n + p - 1) \times (K_n + p)$  difference matrix  $D$  is

$$D = \begin{bmatrix} -1 & 1 & 0 & 0 & \dots & 0 & 0 \\ 0 & -1 & 1 & 0 & \dots & 0 & 0 \\ 0 & 0 & -1 & 1 & \dots & 0 & 0 \\ \dots & & & & \dots & & \\ 0 & 0 & 0 & 0 & \dots & -1 & 1 \end{bmatrix}$$

such that  $D b = [\Delta(b_2), \dots, \Delta(b_{K_n+p})]^T$ , and

$$\lambda = \frac{\lambda^*}{\beta_n}, \quad \Gamma_n = \frac{1}{\beta_n} X^T X, \quad \text{and} \quad \bar{y} = \frac{1}{\beta_n} X^T y,$$

where  $\beta_n \equiv \sum_{i=1}^n B_k^{[p]}(x_i)^2$  for  $k = p+1, \dots, K_n$  and the  $n \times (K_n + p)$  design matrix  $X = [B_k^{[p]}(x_j)]_{k,j}$ . To obtain

the optimality conditions, we introduce more notation. Let  $C$  be the  $(K_n + p - 1) \times (K_n + p)$  matrix given by

$$C = \begin{bmatrix} 1 & 0 & 0 & 0 & \cdots & 0 & 0 \\ 1 & 1 & 0 & 0 & \cdots & 0 & 0 \\ 1 & 1 & 1 & 0 & \cdots & 0 & 0 \\ & \cdots & & \cdots & & & \\ 1 & 1 & 1 & 1 & \cdots & 1 & 0 \end{bmatrix}.$$

Given two vectors  $a$  and  $b$ , we write  $a \geq 0$  (resp.  $b \geq 0$ ) if each component of  $a$  (resp.  $b$ ) is nonnegative and write  $a \perp b$  if  $a$  and  $b$  are orthogonal, i.e.,  $a^T b = 0$ . Hence,  $0 \leq a \perp b \geq 0$  means  $a \geq 0$ ,  $b \geq 0$  and  $a^T b = 0$ . This condition is known as the complementarity condition [2], [13]. The following lemma gives optimality conditions via convex optimization [13], [14]:

**Lemma 3** [14] The vector  $\hat{b}$  is the (unique) optimal solution of (7) if and only if  $0 \leq D\hat{b} \perp C(\bar{y} - \Gamma_n \hat{b}) + \lambda D\hat{b} \geq 0$  and  $\sum_{i=1}^{K_n+p} ((\Gamma_n \hat{b})_i - \bar{y}_i) = 0$ .

It is easy to show that the above optimality conditions are equivalent to the difference equation:

$$\lambda^*(\hat{b}_{j+1} - \hat{b}_j) = \left[ \sum_{k=1}^j \sum_{i=1}^n B_k^{[p]}(x_i) \hat{f}^{[p]}(x_i) - \sum_{k=1}^j \sum_{i=1}^n B_k^{[p]}(x_i) y_i \right]_+ \quad (8)$$

for  $j = 1, \dots, K_n + p - 1$  subject to the boundary condition:

$$\sum_{i=1}^n \hat{f}^{[p]}(x_i) = \sum_{i=1}^n y_i. \quad (9)$$

Since  $(\Gamma_n + \lambda D^T D)$  is positive definite for any  $\lambda > 0$ ,  $\hat{b} = (\hat{b}_1, \dots, \hat{b}_{K_n+p})^T$  is a (vector-valued) continuous piecewise linear function of  $\bar{y}$  [13]. However, the closed form expression of  $\hat{b}$  is hardly obtained due to the combinatorial nature of the complementarity problem and this presents a major technical difficulty for the following development. Despite this difficulty, it is shown that  $\hat{b}(\bar{y}) \in \mathbb{R}^{K_n+p}$  satisfies the uniform Lipschitz property with respect to the  $\ell_\infty$ -norm, regardless of  $K_n$  and  $\lambda$  for all sufficiently large  $n$  (cf. Theorem 4). This property plays a crucial role in establishing stochastic boundedness and uniform consistency of  $\hat{f}^{[p]}$  discussed soon. It should be stressed that this property is different from the conventional Lipschitz property of a linear complementarity problem of *fixed size* [2] since the Lipschitz constant attained here is invariant to size variation.

To obtain a piecewise linear formulation of  $\hat{b}$ , let  $\Lambda_n \equiv (\Gamma_n + \lambda D^T D)/(1+2\lambda)$ ,  $\bar{b} \equiv \hat{b}/(1+2\lambda)$ , and  $z \equiv \bar{y}/(1+2\lambda)$ . Hence the optimality conditions in Lemma 3 become

$$0 \leq D\bar{b} \perp \tilde{C}(\Lambda_n \bar{b} - z) \geq 0 \quad \text{and} \quad \sum_{i=1}^{K_n+p} [(\Lambda_n \bar{b})_i - z_i] = 0, \quad (10)$$

where the  $(K_n + p - 1) \times (K_n + p)$  matrix  $\tilde{C}$  is given by

$$\tilde{C} = \begin{bmatrix} 0 & 1 & 1 & 1 & \cdots & 1 \\ 0 & 0 & 1 & 1 & \cdots & 1 \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 & 1 & 1 \\ 0 & 0 & \cdots & 0 & 0 & 1 \end{bmatrix}$$

For each  $z$ , the corresponding optimal solution  $\bar{b}$  is characterized by an index set  $\alpha = \{i \mid (\tilde{C}(\Lambda_n \bar{b} - z))_i = 0\} \subseteq \{1, \dots, K_n + p - 1\}$  ( $\alpha$  may be empty) via (10). For the given  $\bar{b}$  and  $\alpha$ , define a vector  $\tilde{b}^\alpha$  as follows:  $\tilde{b}_1^\alpha \equiv \bar{b}_1$  and  $\tilde{b}_{i+1}^\alpha \equiv \bar{b}_{\ell_{i+1}}$  for  $i \geq 1$ , where  $\ell_{i+1} \equiv \min_{1 \leq j \leq K_n+p} \{j \mid \bar{b}_j > \tilde{b}_i^\alpha\}$ . Hence, the elements of  $\tilde{b}^\alpha$  strictly increase as their indices increase. Moreover, for each  $\tilde{b}^\alpha$ , define the index set  $\beta_i^\alpha = \{j \in \{1, \dots, K_n + p\} \mid \bar{b}_j = \tilde{b}_i^\alpha\}$ . This gives rise to a (finite and disjoint) partition of  $\{1, \dots, K_n + p\}$ , namely,  $\bigcup_i \beta_i^\alpha = \{1, \dots, K_n + p\}$  and  $\beta_j^\alpha \cap \beta_k^\alpha = \emptyset$  whenever  $j \neq k$ . It can be shown that  $\tilde{b}^\alpha$ , and thus  $\bar{b}^\alpha(z)$  which denotes  $\bar{b}(z)$  corresponding to the index set  $\alpha$ , is a linear function of  $z$ . Hence, for any  $z \in \mathbb{R}^{K_n+p}$ ,  $\bar{b}(z) \in \{\bar{b}^\alpha(z)\}_\alpha$ , where  $\bar{b}^\alpha(z)$  is called a selection function of  $\bar{b}(z)$ . Therefore, the solution mapping  $z \mapsto \bar{b}$  is a (continuous) piecewise linear function with  $2^{(K_n+p)}$  selection functions. The same holds true for the mapping  $\bar{y} \mapsto \hat{b}$ , i.e.,  $\hat{b}_i^\alpha(\bar{y}) \equiv \sum_{j=1}^{K_n+p} \bar{a}_{ij}^\alpha \bar{y}_j$ , where the coefficients  $\bar{a}_{ij}^\alpha$  pertain to each index set  $\alpha$ . By further employing piecewise linear structure, it is shown that under appropriate order conditions on  $n$ ,  $K_n$  and  $\lambda$ , for sufficiently large  $n$  and for any  $K_n \geq 2$  and each  $i$ , each selection function  $\hat{b}_i^\alpha$  satisfies  $|\hat{b}_i^\alpha(\bar{y})| \leq (\sum_{j=1}^{K_n+p} |\bar{a}_{ij}^\alpha|) \max(|\bar{y}_i|) = \kappa_p \|\bar{y}\|_\infty$  for some constant  $\kappa_p > 0$  dependent on  $p$  only, namely, each selection function is Lipschitz continuous with the same Lipschitz constant, regardless of  $K_n$ ,  $\lambda$  and  $\alpha$ . The following theorem summarizes the above discussions whose proof is given in [14]:

**Theorem 4** The following statements hold:

- Let  $p = 0$ . For any  $K_n \geq 2$  and  $\lambda > 0$ ,  $\|\hat{b}(u) - \hat{b}(v)\|_\infty \leq \kappa_0 \|u - v\|_\infty, \forall u, v \in \mathbb{R}^{K_n}$  with  $\kappa_0 = 1$ ;
- Let  $p = 1$ . There exists  $\kappa_1 > 0$  such that for all sufficiently large  $\lambda > 0$  and  $n/K_n$  with  $K_n \geq 2$ ,  $\|\hat{b}(u) - \hat{b}(v)\|_\infty \leq \kappa_1 \|u - v\|_\infty, \forall u, v \in \mathbb{R}^{K_n+1}$ ;
- Let  $p \geq 2$  and  $\varrho \in (0, 1)$ . Suppose  $K_n \sim n^\gamma$  and  $\lambda \sim n^{2(\gamma-\varrho)}$  with  $\gamma \in (\varrho, 1)$ . Then for all  $n$  sufficiently large, there exists  $\kappa_p > 0$  dependent on  $p$  only such that  $\|\hat{b}(u) - \hat{b}(v)\|_\infty \leq \kappa_p \|u - v\|_\infty, \forall u, v \in \mathbb{R}^{K_n+p}$ .

Define  $\check{b} \equiv \hat{b}(E(\bar{y}_n))$  and  $\bar{f}^{[p]}(x) \equiv \sum_{k=1}^{K_n+p} \check{b}_k B_k^{[p]}(x)$ . By Theorem 4,

$$\begin{aligned} \sup_{x \in [0,1]} |\hat{f}^{[p]}(x) - \bar{f}^{[p]}(x)| &\leq \|\hat{b}(\bar{y}_n) - \check{b}(E(\bar{y}_n))\|_\infty \\ &\leq \kappa_p \|\bar{y}_n - E(\bar{y}_n)\|_\infty = O_p(\sqrt{n^{-1} K_n \log K_n}) \end{aligned} \quad (11)$$

Let  $\alpha \equiv \frac{\lambda^*}{nK_n}$ . It is shown that, under mild conditions on  $f$ ,

$$\sup_{x \in [0,1]} |\bar{f}^{[p]}(x) - f(x)| = \begin{cases} O(\alpha) & \text{if } p = 1 \\ O(\alpha) + O(\frac{1}{K_n}) & \text{if } p \neq 1 \end{cases} \quad (12)$$

The development of (12) is a special case of Theorem 5 in Section IV-B. Combining (11) and (12), we have (i)  $\sup_{x \in [0,1]} |\hat{f}^{[p]}(x) - f(x)| = O_p(\sqrt{n^{-1} K_n \log K_n}) + O(\alpha)$  if  $p = 1$ , and (ii)  $\sup_{x \in [0,1]} |\hat{f}^{[p]}(x) - f(x)| = O_p(\sqrt{n^{-1} K_n \log K_n}) + O(\alpha) + O(\frac{1}{K_n})$  if  $p \neq 1$ . This result shows that  $\hat{f}^{[p]}$  is stochastically uniformly bounded

and  $\hat{f}^{[p]}(0)$  is consistent if  $K_n \log K_n/n \rightarrow 0$  and  $\alpha \rightarrow 0$  as  $K_n \rightarrow \infty$  and  $n \rightarrow \infty$ .

### B. Asymptotic Property of the Monotone P-spline Estimator

1) *Linear Splines:  $p = 1$ :* We first derive the asymptotic distribution of  $\hat{f}^{[p]}$  when  $p = 1$ . The closed form representation of  $\hat{f}^{[1]}$  based on (8) cannot be obtained, making it difficult to study its properties. In this section, we replace the difference equation (8) by its analogous differential equation to study its asymptotic distributions.

Let  $\omega$  be the uniform distribution on  $x_1, \dots, x_n$  and let  $g$  be the piecewise constant function for which  $g(x_i) = y_i$  for  $i = 1, \dots, n$ . Define  $\hat{F}(x) = \int_0^x \hat{f}^{[1]}(y)dy$  and  $G(x) = \int_0^x g(y)d\omega(y)$ . Denote  $\tilde{G}$  the greatest convex minorant of the cumulative sum diagram  $G$ . It is proved in [10] that  $G$  and  $\tilde{G}$  are close when  $f$  is strictly increasing and its derivative is bounded away from zero, and  $\|G - \tilde{G}\| = O_p((n^{-1} \log n)^{2/3})$ , where  $\|f\| \equiv \sup_{[0,1]} |f(x)|$ . The subsequent norms in this section are defined in the same way. For any  $x \in (0, 1)$ , let  $d = \lfloor K_n x \rfloor$ . It is clear that  $\hat{F}''(x) = K_n(\hat{b}_{d+2} - \hat{b}_{d+1})$ . Let

$$R_1(x) \equiv [\hat{F}(x) - G(x)] - \left[ \frac{1}{n} \sum_{k=1}^{d+1} \sum_{i=1}^n B_k^{[1]}(x_i) \hat{f}(x_i) - \frac{1}{n} \sum_{k=1}^{d+1} \sum_{i=1}^n B_k^{[1]}(x_i) y_i \right].$$

Recalling  $\alpha = \frac{\lambda^*}{nK_n}$ , equation (8) becomes  $\alpha \hat{F}'' = [\hat{F} - G - R_1]_+$ . Define  $R_2 \equiv (\hat{F} - \tilde{G}) - \alpha \hat{F}''$ . Then  $\hat{F}$  solves the differential equation

$$\alpha \hat{F}''(t) = \hat{F}(t) - \tilde{G}(t) - R_2(t), \quad t \in [0, 1], \quad (13)$$

with two boundary conditions  $\hat{F}(0) = 0$  and  $\hat{F}(1) = \tilde{G}(1) + e_1$  by (9), where  $e_1 = \hat{F}(1) - \tilde{F}(1)$  is of order  $O_p(1/n)$  since  $\hat{f}^{[1]}$  is bounded with probability one by (11) and (12). It can be shown that  $\|R_2\|$  is small and of order  $O_p((n^{-1} \log n)^{2/3}) + O_p((n^{-1} K_n^{-1} \log K_n)^{1/2})$ .

Denote  $\xi = 1/\sqrt{\alpha}$ . The solution to (13) can be expressed explicitly by the corresponding Green's function [11]

$$\chi_\alpha(t, s) = \frac{1}{2} \xi e^{-\xi|t-s|}, \quad 0 \leq t \leq 1 \quad (14)$$

Using this, we have

$$\hat{F}(x) = \int_0^1 \chi_\alpha(x, s) \tilde{G}(s) ds + \int_0^1 \chi_\alpha(x, s) R_2(s) ds + c_0(\xi) e^{-\xi x} + c_1(\xi) e^{-\xi(1-x)},$$

where both  $c_0$  and  $c_1$  can be obtained from the boundary conditions and it can be shown that  $|c_0(\xi)| + |c_1(\xi)| \leq 6\|\tilde{G} + R_2\| + 4\|\hat{F}\|$  for  $\xi \geq 1$ .

**Theorem 5** [14] Assume that the true regression function  $f$  is twice continuously differentiable. Then  $\hat{f}$  is given by

$$\hat{f}^{[1]}(x) = f(x) + \alpha f''(x) + o(\alpha) + \frac{\xi}{2n} \sum_{i=1}^n e^{-\xi|x-x_i|} \epsilon_i + O_p\left(\left(\frac{n}{\log n}\right)^{-2/3}\right) \xi + O_p\left(\left(\frac{\log K_n}{nK_n}\right)^{1/2}\right) \xi + e^{-\xi x(1-x)} O_p(\xi)$$

uniformly in  $\lambda$  and  $x \in (0, 1)$ . Moreover, if  $f$  is three times continuously differentiable, then

$$\begin{aligned} \frac{d}{dx} \hat{f}^{[1]}(x) &= f'(x) + \alpha f'''(x) + o(\alpha) + O_p\left(\frac{1}{\sqrt{n\xi}}\right) \\ &\quad + O_p\left(\left(\frac{n}{\log n}\right)^{-2/3}\right) \xi^2 + O_p\left(\left(\frac{\log K_n}{nK_n}\right)^{1/2}\right) \xi^2 \\ &\quad + e^{-\xi x(1-x)} O_p(\xi^2) \end{aligned}$$

uniformly in  $\lambda$  and  $x \in (0, 1)$ .

Theorem 5 indicates that the monotone P-spline estimator is approximately a kernel regression estimator. The equivalent kernel is the double-exponential or Laplace kernel and its bandwidth is of order  $\alpha$ . The asymptotic mean has the bias  $\alpha f''(x) + o(\alpha)$ , which can be negligible if  $\alpha$  is reasonably small. However,  $\alpha$  cannot be arbitrarily small as that will inflate the random component. The admissible range for  $\alpha$  given in Theorem 6 is a compromise between these two.

**Theorem 6** [14] Suppose that  $f$  is twice continuously differentiable with bounded second order derivative on  $[0, 1]$ .

(a) If  $\alpha$  and  $K_n$  satisfy  $\alpha n^{2/3} \rightarrow \infty$ ,  $\alpha n^{2/5} \rightarrow 0$ , and  $\alpha^{-1/2} \log K_n / K_n \rightarrow 0$ , then

$$\sqrt{n\alpha^{1/2}} (\hat{f}^{[1]}(x) - f(x)) \rightarrow N\left(0, \frac{\sigma^2}{4}\right) \quad (15)$$

in distribution as  $n \rightarrow \infty$ .

(b) If  $\alpha = c^2 n^{-2/5}$  and let  $K_n \sim n^\gamma$  with  $\gamma > 1/5$ , then

$$n^{2/5} (\hat{f}^{[1]}(x) - f(x)) \rightarrow N\left(c^2 f''(x), \frac{\sigma^2}{4c}\right) \quad (16)$$

in distribution as  $n \rightarrow \infty$ .

2) *Splines of Other Degrees:  $p \neq 1$ :* In this section, we study the asymptotic property of  $\hat{f}^{[p]}(x) = \sum_{k=1}^{K_n+p} \hat{b}_k B_k^{[p]}(x)$  when  $p \neq 1$ . We first define a piecewise linear function  $\tilde{f}^{[p]}$ , where  $\hat{f}^{[p]}$  and  $\tilde{f}^{[p]}$  share the same set of spline coefficients. In particular, define  $\tilde{f}^{[0]}(x) = \sum_{k=1}^{K_n} \hat{b}_k B_k^{[1]}(x)$ , and  $\tilde{f}^{[p]}(x) = \sum_{k=1}^{K_n+1} \hat{b}_k^{[p]} B_k^{[p]}(x)$  if  $p \geq 2$ . Note that  $\tilde{f}^{[0]}$  is defined on  $[0, 1 - \frac{1}{K_n}]$ . Denote  $\tilde{F}(x) = \int_0^x \tilde{f}^{[p]}(y)dy$ . For any  $x \in (0, 1)$ , let

$$R_3(x) \equiv [\tilde{F}(x) - G(x)] - \frac{1}{n} \left[ \sum_{k=1}^{d+1} \sum_{i=1}^n B_k^{[p]}(x_i) \tilde{f}(x_i) - \sum_{k=1}^{d+1} \sum_{i=1}^n B_k^{[p]}(x_i) y_i \right].$$

Thus the optimality condition (8) becomes  $\alpha \tilde{F}''(x) = [\tilde{F} - G - R_3]_+$ . Define  $R_4 \equiv (\tilde{F} - \tilde{G}) - \alpha \tilde{F}''$ . Then  $\tilde{F}$  solves the differential equation

$$\alpha \tilde{F}''(t) = \tilde{F}(t) - \tilde{G}(t) - R_4(t), \quad t \in [0, 1], \quad (17)$$

with two boundary conditions  $\tilde{F}(0) = 0$  and  $\tilde{F}(1) = \tilde{G}(1) + e_2$ , where  $e_2 = O_p(1/n)$ . Following the same discussion as in Section IV-B.1, we can establish the asymptotic distribution for  $\tilde{f}^{[p]}$  as in (15) and (16), respectively, under different admissible ranges of  $\alpha$  and  $K_n$ .

**Theorem 7** [14] Suppose that  $f$  is three times continuously differentiable with bounded  $f'''$  on  $[0, 1]$ . Let  $p \neq 1$ .

(a) If  $\alpha$  and  $K_n$  satisfy  $\alpha n^{2/3} \rightarrow \infty$ ,  $\alpha n^{2/5} \rightarrow 0$ , and  $\alpha^{-1/2} \log K_n / K_n \rightarrow 0$ , then

$$\sqrt{n\alpha}^{\frac{1}{2}} \left( \hat{f}^{[p]}(x) - f(x) - r_n^{[p]}(x) \right) \longrightarrow N\left(0, \frac{\sigma^2}{4}\right)$$

in distribution as  $n \rightarrow \infty$ , where (i)  $r_n^{[p]}(x) = -\frac{1}{2K_n} f'(x)$  if  $p = 0$  and (ii)  $r_n^{[p]}(x) = f'(x) \sum_{q=2}^p \sum_{i=d+2}^{d+q+1} \frac{1}{q} (x - \kappa_{i-q}) B_i^{[q-1]}(x)$  if  $p \geq 2$ ;

(b) If  $\alpha = c^2 n^{-2/5}$  and let  $K_n \sim n^\gamma$  with  $\gamma > 1/5$ , then

$$n^{\frac{2}{5}} \left( \hat{f}^{[p]}(x) - f(x) - r_n^{[p]}(x) \right) \longrightarrow N\left(c^2 f''(x), \frac{\sigma^2}{4c}\right)$$

in distribution as  $n \rightarrow \infty$ .

## V. NUMERICAL EXAMPLE

To illustrate the proposed estimator, we consider a simplified model of a carbon starvation network in *E. coli* [4]. This network, which is of the form given by (2), consists of four state variables with  $\gamma_1 = 0.75, \gamma_2 = 1.5, \gamma_3 = 2, \gamma_4 = 0.75$ , and  $k_1 = 0.2, k_2 = 0.85, k_3 = 0.75, k_4 = 0.6$ . The interval  $\mathcal{I}$  is scaled as  $[0, 1]$  and  $\theta = 0.5$ . The time step  $\tau = 0.01$ . We assume that  $z(k)$  is not available but  $v(k) \equiv x_1(k)$  is. Hence Assumptions 1–3 hold true for the system. A quadratic B-spline basis is used in the monotone  $P$ -spline estimation, i.e.,  $p = 2$  in equation (6). Figure 2 shows the plot of input vs. output for monotone estimation, and Figures 3 and 4 display the monotone  $P$ -spline and monotone least-square estimations respectively. The monotone least-square estimator yields a piecewise constant estimation while the  $P$ -spline estimator gives a much smoother result and thus outperforms the former. Other widely used estimators, e.g. [8], do not guarantee monotonicity and thus are omitted.

## VI. CONCLUSION

In this paper, a two-stage procedure is developed to estimate a monotone function in a dynamical system. The first stage uses the trend filtering based partial state estimation, and the second stage uses the monotone  $P$ -spline estimation. This approach is applied to estimation of a monotone regulatory function in a gene network. Extension of this approach to more general constraints (e.g. the Luré-type constraint) and dynamics is currently under investigation.

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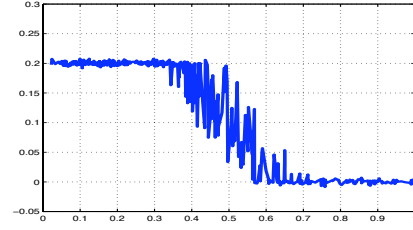


Fig. 2. Input vs. output for monotone estimation

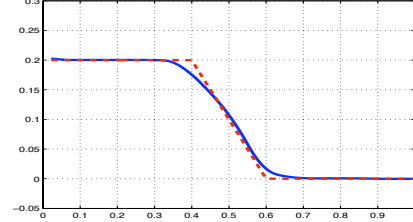


Fig. 3. Solid line:  $P$ -spline estimation ( $p = 2$ ); dashed line: true function

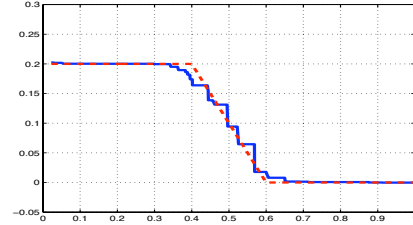


Fig. 4. Solid line: least-square estimation; dashed line: true function

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