Nonparametric deconvolution of hormone time-series:
A state-space approach*

Giuseppe De Nicolao, Giancarlo Ferrari Trecate, Marco Franzosi
Dipartimento di Informatica e Sistemistica
Università degli Studi di Pavia
Via Ferrata 1
27100 Pavia (Italy)
Tel: +39 382 505484
Fax: +39.382.505373
E-mail: {denicolao,ferrari}@conpro.unipv.it

Abstract
The instantaneous secretion rate (ISR) of endocrine glands is not directly measurable and it can be reconstructed only indirectly by applying deconvolution algorithms to time-series of plasma hormone concentrations. In particular, nonparametric regularization-based deconvolution hinges on a variational problem whose solution is usually approximated by discretizing the continuous-time axis. The paper shows how to perform regularized deconvolution avoiding any form of discretization. In view of the equivalence between regularization and Bayesian estimation, it is seen that the estimated ISR is a weighted sum of N basis functions, where N is the number of data. State-space methods are used to derive analytically the basis functions as well as the entries of the matrix of the linear system used to compute the weights. Alternatively, the weights can be computed in O(N) operations by a suitable algorithm based on Kalman filtering. As an illustration of the method, we estimate the spontaneous pulsatile ISR of luteinizing hormone (LH) from time series of plasma LH concentrations sampled every 5 min.

Keywords: Endocrinology, Hormones, Deconvolution, Smoothing, Estimation, Kalman filtering, neural networks.

1. Introduction
The knowledge of the glandular secretory activity is essential in order to understand the complex feedforward/feedback interactions of the endocrine system. However, the flux of hormone from the gland to the circulation is not directly measurable. It is only possible to obtain time-series of hormone concentrations measured in blood samples withdrawn at some given instants. In most cases the hormone flux entering the circulation and the plasma hormone concentration can be adequately modeled as the input and the output of a linear time-invariant system. Then, the ISR (instantaneous secretion rate) of the gland can be traced back by solving a deconvolution problem.

To make an example, consider the LH (Luteinizing Hormone), which plays an essential role in reproduction physiology and is secreted by the hypophysis. In order to assess its spontaneous secretion, a typical experiment involves collecting blood samples with a 5 min sampling period over several hours (from 6 to 24). Since LH (as most other hormones) is produced according to an episodic pulsatile pattern, the possible parameters of interest are the number, the amplitude, and the duration of the ISR pulses [12]. The concentration data cannot be used to directly assess the gland activity because the plasma LH concentration at a given instant is the result of all the secretory activity occurred before. The same kind of problems arise in the analysis of the spontaneous secretion of other hormones such as FSH, ACTH, Cortisol, Testosterone, etc, see e.g. [4], [15].

There are some specific features that render the deconvolution of hormone time-series a nontrivial task. Among them, the ill-conditioning of the inverse problem, the infrequent and possibly nonuniform sampling rate, the presence of nonnegativity constraints. In order to cope with these difficulties, several methods have been proposed including discrete deconvolution, [3], parameter optimization [14], and, more recently, nonparametric regularization-based deconvolution [6], [5], [10]. In the regularization approach, the input is estimated as the minimizer of a cost functional which is the sum of the least-squares fit and a smoothness penalty, e.g. the integral

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of the squared first (or second) derivative of the input. The actual computation is carried out by discretizing the unknown input over a frequent grid (called "virtual" to distinguish it from the sampling grid of the measurements). Although, such an algorithm has been shown to perform effectively in a number of cases [6], [10], it is only approximated and its accuracy depends on the choice of a sufficiently fine virtual grid.

The main purpose of the present paper is to develop explicit formulas for the calculation of nonparametric regularized deconvolution avoiding any form of discretization. In fact, by exploiting the equivalence of regularization and Bayesian estimation, it is easy to see that the solution of the variational problem has the structure of a regularization network, [9] i.e. it is a weighted sum of N basis functions. A first contribution of the paper is the derivation (by state-space methods) of these basis functions when the impulse response of the system is a linear combination of exponentials (as happens for hormone time-series). State space techniques play an important role also in the calculation of the weight vector, whose calculation as the solution of a system of N linear equations would require O(N^3) operations. As a matter of fact, we show that the weights can be computed in O(N) operations by means of a Kalman filtering algorithm. Finally, to show that the weights can be computed in O(N) operations, when the impulse response of the system is a linear combination of exponentials (as happens for hormone time-series). State space techniques play an important role also in the calculation of the weight vector, whose calculation as the solution of a system of N linear equations would require O(N^3) operations. As a matter of fact, we show that the weights can be computed in O(N) operations by means of a Kalman filtering algorithm. Finally, to demonstrate the effectiveness of the proposed method, we consider the deconvolution of time-series of plasma LH concentrations with 5-min sampling period.

2. Problem Statement and Basic Assumptions

According to the literature, see e.g. [4], [12] and references quoted therein, a fairly accurate model of the hormone concentration dynamics is given by the convolution integral

\[ z(t) = \int_{t-\tau}^{t} g(t-\tau) u(\tau) d\tau \]  

(1)

where \( g(t) \) denotes the hormone elimination rate, and \( u(t) \) (mIU/ml min.) is the hormone ISR, both normalized by the circulation volume, while \( z(t) \) (mIU/ml) is the hormone plasma concentration. In other words, \( g(t) \) is the impulse response of the dynamical system, i.e. the hormone concentration that would be observed if, in absence of endogenous secretion, a unitary intravenous hormone injection were made at time zero.

\[ \begin{align*}
\text{unknown} & \quad \text{unknown} \\
\text{LTI System} & \quad \text{plasma} \\
g(t) & \quad z(t) \\
\end{align*} \]

\[ \begin{align*}
\begin{array}{c}
\text{endo} \\
\text{secretion} \\
\text{rate} \\
\end{array} & \quad \begin{array}{c}
\text{plasma} \\
\text{concentration} \\
\text{measurements} \\
\end{array}
\end{align*} \]

Fig. 1: Block diagram of the deconvolution problem; \( u(t) \), unknown glandular secretion rate; \( z(t) \): plasma hormone concentration; \( y_k \): discrete noisy measurements.

In the endocrinological literature it has been found that a good model for \( g(t) \) is given by a weighted sum of exponentials:

\[ g(t) = \sum_{i=1}^{L} a_i e^{-\alpha_i t} \]  

(2)

Usually, \( L \leq 3 \). The parameters \( a_i \) and \( \alpha_i \) depend on the specific hormone (and possibly also on the pathophysiological conditions of the patient). A table summarizing the estimated population parameters for several hormones (GH, ACTH, PRL, LH, TSH, Cortisol, FSH) is reported in [4].

Depending on the type of experiment, a number of blood samples ranging from 5 to some hundreds are withdrawn. The sampling grid can be nonuniform, with sampling intervals ranging from 1 min. to 30 min. Due to the measurement errors the actual samples \( y_k \) (mIU/ml) are given by

\[ y_k = z(t_k) + v_k, \quad k = 1, 2, ..., N \]  

(3)

where the errors \( v_k \) are zero-mean, independent and normally distributed, with \( \text{Var}(v_k) > 0, \quad \forall \ k \). In general \( t_0 = -\infty \), although from a computational point of view it suffices that \( t_1 - t_0 \gg 0 \) (compared to the system time constants).

From the statement of the problem, it is apparent that the ISR estimation problem amounts to reconstructing the input of a linear system, given noisy samples of the output. In the literature, a number of deconvolution methods have been proposed, see [6] for a discussion. In particular, the regularization method [11] is based on the cost functional

\[ J_y(u) = \sum_{k=1}^{N} \frac{(y_k - z(t_k))^2}{\text{Var}(v_k)} + \gamma \int_{t_0}^{t_1} \left( \frac{du(\tau)}{d\tau} \right)^2 d\tau \]  

(4)

where the positive real number \( \gamma \) is the so-called regularization parameter which controls the trade-off between fidelity to the data and smoothness of the solution. Among the possible criteria for the tuning of this parameter one may cite GCV (Generalized Cross Validation) [16] and ML (Maximum Likelihood) [8], [6]. The regularized estimate is defined as the solution of the variational problem

\[ \hat{u}(\cdot) = \arg \min_{u(\cdot)} J_y(u) \]  

(5)

The standard way to compute \( \hat{u}(\cdot) \) is to discretize the unknown function \( u(\cdot) \) and reformulate (4), (5) as a quadratic optimization problem where the unknown is a vector, whereas the convolution integral (1) is approximated by a matrix-vector product. Then the solution is found by solving a system of linear equations, with complexity \( O(N^3) \), see e.g. [6]. We end this section by pointing out a Bayesian interpretation of the estimator (5), which will be useful in the following. Hereafter, the vector of experimental data will be denoted by \( \gamma = [y_1 y_2 \ldots y_N]^T \). The following proposition is a corollary of Theorem 1.5.2. in [16].

**Proposition 1:** Assume that

\[ (i): \quad u(t) = \int_{\tau}^{t} w(\tau) d\tau, \quad \text{where} \ w(\cdot) \ \text{is a continuous-time} \]

WGN (White Gaussian Noise), independent on \( y_k \), with intensity \( \lambda^2 \).
(ii): \( \gamma = \frac{1}{\lambda^2} \).

Then, the regularized solution \( \hat{u}^*(t) \) coincides with the conditional expectation (Bayes estimate)
\[
\hat{u}^*(t) = E[u(t)|y] = E[u(t)Y^T]E[Y^TY]^{-1}Y. \tag{6}
\]

3. A State-Space Deconvolution Formula

In this section it will be shown that the particular structure (2) of the impulse response \( g(t) \) can be exploited in order to derive an efficient computational algorithm that completely avoids discretization. To this purpose, consider the following stochastic state-space representation:
\[
\begin{align*}
\dot{x} &= Ax + Bu \\
y &= Cx(t) + v
\end{align*} \tag{7}
\]

where \( A, B, C \) are block matrices defined as follows
\[
A = \begin{bmatrix}
1 & -\alpha_1 & 0 & \cdots & 0 \\
1 & 1 & -\alpha_2 & \cdots & 0 \\
\vdots & \vdots & \ddots & \ddots & \vdots \\
1 & \cdots & 1 & -\alpha_{L-1} & 0 \\
\end{bmatrix}, \\
B = \begin{bmatrix}
0 \\
0 \\
\vdots \\
0 \\
\end{bmatrix}, \\
C = \begin{bmatrix}
0 & \cdots & 0 & 1 \\
\end{bmatrix}, \\
F = \text{diag}\{\alpha_i\}, \\
G = \begin{bmatrix}
H \\
\vdots \\
H \\
\end{bmatrix}.
\]

Under the assumptions of Proposition 1, it is easy to see that \( u(t) = x_t(t) \) and \( z(t) = Cx(t) \).

Given the state-space representation (7), (8) a possible way to estimate \( u(t) \) is to resort to optimal state-space smoothing algorithms [2]. Herein, however, we follow a different approach that leads to a simple analytic form for the estimate. Recalling that \( u(t) = x_t(t) \), the following result is a straightforward consequence of Proposition 1.

Proposition 2: Under the assumptions of Proposition 1,
\[
\hat{u}^*(t) = \sum_{i=1}^{N} \phi_i(t) \tag{9}
\]

where \( \phi_i(t) = E[x(t)\phi(t)] \) and the vector \( \vartheta = [\vartheta_1, \vartheta_2, \ldots, \vartheta_N]^T \) satisfies the equation
\[
E[Y^TY]\vartheta = Y. \tag{10}\]

Observe that the estimate (9) has the structure of a so-called regularization neural network [9], where \( \phi_i(t), i = 1, \ldots, N \) are the basis functions with corresponding weights \( \vartheta_i, i = 1, \ldots, N \).

An advantage of the network (9) is that, if different experiments are carried out using the same sampling grid, the functions \( \phi_i(t) \) and the structure of the matrix \( E[Y^TY] \) remain unchanged. Then, each continuous-time estimate is completely characterized by its specific \( N \)-dimensional weight vector \( \vartheta \).

In the following, two main results will be derived:

(i) an analytical expression for \( \phi(t) \) and \( E[Y^TY] \) will be worked out;
(ii) it will be shown how to compute \( \theta \) in \( O(N) \) operations (instead of \( O(N^2) \)).

In order to fulfill the first objective, two preliminary lemmas are needed.

Lemma 1: Let \( A \) be as in (8). Then
\[
e^{-\alpha t} = \begin{bmatrix}
\frac{1}{G(t)} & 0 \\
0 & \frac{1}{e^{\alpha T}}
\end{bmatrix} \tag{11.a}
\]

where
\[
\begin{align*}
\tilde{G}(t) &= \begin{bmatrix}
\tilde{G}_1(t) & \tilde{G}_2(t) & \cdots & \tilde{G}_L(t)
\end{bmatrix} \\
\tilde{G}_i(t) &= \frac{1-e^{-\alpha_{i+1}}}{\alpha_i} \\
e^{\alpha t} &= \text{diag}\{e^{\alpha_i t}\} \tag{11.b}
\end{align*}
\]

Lemma 2: Let \( X(t) = E[x(t)x(t)^T] \). Then
\[
X(t) = \lambda^2 \begin{bmatrix}
-t-t_0 & \vartheta(t)^T \\
\vartheta(t) & \bar{X}(t)
\end{bmatrix} \tag{12}
\]

where
\[
\vartheta(t) = \begin{bmatrix}
1 & t-t_0 + \frac{e^{\alpha_{i+1}t}}{\alpha_i} - 1 \\
\alpha_i & \alpha_i + \alpha_j + \alpha_{i+1}
\end{bmatrix}
\]

\[
\bar{X}(t) = \begin{bmatrix}
1 & t-t_0 + \frac{e^{\alpha_{i+1}t}}{\alpha_i} - 1 \\
\alpha_i & \alpha_i + \alpha_j
\end{bmatrix}
\]

\[
\lambda^2 \int_{t_0}^{t} e^{\alpha_{i+1}t}BB^Te^{\alpha_{i+1}t}dt = \lambda^2 \int_{t_0}^{t} e^{\alpha_{i+1}t}BB^Te^{\alpha_{i+1}t}dt \tag{13}
\]

Then, in view of Lemma 1, the thesis straightforwardly follows by simple computations.

Theorem 1: With reference to Proposition 2, the basis functions \( \phi_k(t), k = 1, 2, \ldots, N \) are given by
\[
\phi_k(t) = \begin{bmatrix}
\lambda^2 \vartheta(t)^T H^T \\
\lambda^2 \left[ (t-t_0) \tilde{G}(t_k-t)^T H^T + (t-t_0) \tilde{G}(t_k-t)^T H^T \right]
\end{bmatrix}, t > t_k
\]

\[
\phi_k(t) = \begin{bmatrix}
\lambda^2 \vartheta(t)^T H^T \\
\lambda^2 \left[ (t-t_0) \tilde{G}(t_k-t)^T H^T + (t-t_0) \tilde{G}(t_k-t)^T H^T \right]
\end{bmatrix}, t_0 \leq t \leq t_k \tag{14}
\]

Proof: First, observe that
where \( y_c \) is a realization of \( (16) \). Conversely, if \( \phi_k = \begin{bmatrix} 1 & 0_{L,L} \end{bmatrix} X(t_k) e^{\Delta(t_k)} C^T \), then the thesis follows in view of Lemmas 1 and 2.

**Theorem 2:** With reference to Proposition 2, the matrix \( E(Y(t)Y(t)^T) \) is given by: \( E(Y Y^T) = \Sigma + \text{diag} \{ \text{Var} [v_k] \} I_j \), where

\[
\Sigma = \mathbb{E} \left[ z(t_j) z(t_j)^T \right] = \left\{ \begin{array}{c} \lambda^2 H \left[ G(t_j - t_j) \bar{x}(t_j)^T + e^{\Delta(t_j)} \bar{x}(t_j) \right] H^T, \quad t_j \geq t_j \\ \Sigma_{ij}, \quad t_i < t_j \end{array} \right. \]

**Proof:** If \( t_j \geq t_i \), we have that \( \mathbb{E} \left[ z(t_i) z(t_i)^T \right] = \mathbb{E} \left[ x(t_i) x(t_i)^T \right] C^T = C e^{\Delta(t_i)} X(t_i) C^T \). Analogously, if \( t_i < t_j \),

\[
\mathbb{E} \left[ z(t_i) z(t_i)^T \right] = C X(t_i) e^{\Delta(t_i)} C^T
\]

Then the thesis follows by applying Lemmas 1 and 2.

4. **Weight Calculation via Kalman Filtering**

In general, the calculation of the weight vector \( \vartheta \) through the solution of the system of linear equations (10) would require \( O(N^2) \) operations. In this section an efficient \( O(N) \) algorithm based on a Kalman filter is derived.

To this purpose, a definition and a technical lemma are first introduced.

**Definition:** In the following, the linear time-varying discrete-time system

\[
x_{k+1} = A_k x_k + B_k u_k \quad x_1 = 0 \quad \text{(16a)}
\]

\[
y_k = C_k x_k + D_k u_k \quad k = 1, 2, \ldots, N \quad \text{(16b)}
\]

where \( u_k, y_k \in \mathbb{R}^j \), is said to be a realization of the matrix \( M \in \mathbb{R}^{M \times N} \) if

\[
\begin{bmatrix} y_1 & y_2 & \cdots & y_N \end{bmatrix}^T = M \begin{bmatrix} u_1 & u_2 & \cdots & u_N \end{bmatrix}^T.
\]

**Lemma 3:** Assume that (16) is a realization of \( M \). Then, the system

\[
\begin{aligned}
\xi_{k-1} &= A_k^T \xi_k + C_k^T u_k \\
\eta_k &= B_k^T \xi_k + D_k u_k \\
\end{aligned} \quad k = 0, N-1, \ldots, 1
\]

is a realization of \( M^T \), in the sense that

\[
\begin{bmatrix} \eta_1 & \eta_2 & \cdots & \eta_N \end{bmatrix}^T = M^T \begin{bmatrix} u_1 & u_2 & \cdots & u_N \end{bmatrix}^T
\]

**Proof:** By inspection.

**Theorem 3:** Consider the stochastic system (7), and let \( \vartheta = [\vartheta_1 \ \vartheta_2 \ \cdots \ \vartheta_N] \) be a solution of \( E(Y Y^T) \vartheta = Y \).

Then, \( \vartheta \) can be computed by means of the following \( O(N) \) algorithm:

\[
\begin{aligned}
\xi_{k+1} &= \begin{bmatrix} e^{\alpha_k} - 1 \\ e^{\alpha_k} - 1 \end{bmatrix} K_k \overline{e}_k + K_k y_k \\
\eta_k &= R_k^{1/2} (y_k - C_k \overline{e}_k) \\
\end{aligned} \quad k = 1, 2, \ldots, N
\]

\[
\begin{aligned}
\vartheta_1 &= K_1 \overline{e}_1 + R_1^{1/2} \eta_1, \quad \vartheta_i = K_i \overline{e}_i + R_i^{1/2} \eta_i, \quad k = N, N-1, \ldots, 1
\end{aligned}
\]

where

\[
\begin{aligned}
P_{i+1} &= e^{\alpha_{i+1}} P_i e^{\alpha_{i+1}} - K_i R_i K_i^T \\
Q_k &= \lambda \int_{t_i}^{t_{i+1}} e^{\alpha_{i+1}} - 1 e^{\alpha_{i+1}} - 1 d \tau \\
R_k &= C P_k C^T + \text{Var} [v_k] \\
K_k &= e^{\alpha_{i+1}} P_i C^T R_k^{-1}
\end{aligned}
\]

**Proof:** That (17.a) is just the 1-step Kalman prediction for the discrete-time system obtained by sampling the continuous-time stochastic system (7). In particular, \{\overline{e}_k\} is the sequence of the normalized innovations. By a well-known property of Kalman filtering theory [1], the innovations sequence is white so that, letting \( \eta = [\eta_1 \ \eta_2 \ \cdots \ \eta_N] \), it follows that \( E(\eta \ \eta^T) = I \). Now let \( \Gamma \) be the matrix such that \( \eta = \Gamma Y \) (in other words, (17) is a realization of \( \Gamma \)). Then

\[
I = E(\eta \ \eta^T) = E(\Gamma Y Y^T \Gamma^T) = \Gamma E(\ Y Y^T) \Gamma^T
\]

which easily implies \( E(\eta \ \eta^T) = \Gamma \Gamma^T \).

Hence, letting \( \vartheta \) be defined by (17)-(18), we conclude that \( \vartheta = \Gamma^T \Gamma Y = E(\ Y Y^T)^T \). Y.

5. **Deconvolution of LH data**

The algorithm worked out in the previous sections has been tested on a time-series of plasma LH (luteinizing hormone) concentrations in a normal subject consisting of the samples \( y_k, k = 1, \ldots, 40 \), collected with a uniform 5-min sampling period (\( t_j = 5(k-1) \)) [7]. To ease the comparison with the discretization approach to nonparametric deconvolution, we analyze the same set of data presented in [6].

The impulse response describing the hormone decay in the circulation is given by the second-order model (L=2):

\[
g(t) = a_1 e^{-\alpha_1 t} + a_2 e^{-\alpha_2 t}\]

where \( a_1, a_2, \alpha_1, \alpha_2 \) are population values (\( a_1 = 0.615 \text{ mIU mL}^{-1} \), \( a_2 = 0.385 \text{ mIU mL}^{-1} \), \( a_1 = 3.87 \cdot 10^{-2} \text{ min}^{-1} \), \( a_2 = 7.69 \cdot 10^{-3} \text{ min}^{-1} \), where mIU stands for milli-International-Unit, see [13]). The meas-
measurement error has a constant Coefficient of Variation, namely $\text{Var}[v_k] = \sigma^2 x^2_k$, where $\sigma = 5.2\%$ is the coefficient of variation. Since spontaneous secretion is studied, $u(t) \neq 0$, $t < 0$, which has been kept into account by letting $t_0 = -55$ min.

The regularization parameter was adjusted so as to obtain the same degree of smoothness as in a previous study [6]. This was achieved by tuning $\gamma$ until the equivalent degree of freedom $q(\gamma)$ was equal to 16.6 (for the definition and a discussion of the role of $q(\gamma)$ in the optimal tuning of $\gamma$ the interested reader is referred to [6]).

The results are reported in Fig. 2. In the upper panel, the measured concentrations are plotted together with the continuous-time concentration profile reconstructed by reconvoluting the estimated ISR, which in turn is reported in the lower panel. The pulsatile nature of the ISR is apparent. In particular it is easy to distinguish 4-5 major secretory episodes as well as some minor ones.

A comparison with Fig. 1 in [6] does not show any appreciable difference with respect to the estimates obtained by discretization. Nevertheless, such a discretization had been carried out on a rather frequent virtual grid (1-min sampling corresponding to a 250x1 unknown vector) which entails a significant computational burden. On the contrary, the new deconvolution procedure does not use any discretization and is computationally more efficient.

![Deconvolution of LH data. Upper panel: measured LH concentrations in plasma (circles) and reconstructed continuous-time concentration profile (-). Lower panel: estimated ISR.](image)

6. References


