On Identification of Biological Systems

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Abstract

System identification finds nowadays application in various areas of biological research as a tool of empiric mathematical modeling and model individualization. A fundamental challenge of system identification in biology awaits in the form of response variability. Furthermore, biological systems tend to exhibit high degree of nonlinearity as well as significant time delays. This thesis covers system identification approaches developed for the applications within two particular biomedical fields: neuroscience and endocrinology.

The first topic of the thesis is parameter estimation of the classical Elementary Motion Detector (EMD) model in insect vision. There are two important aspects to be taken care of in the identification approach, namely the nonlinear dynamics of the individual EMD and the spatially distributed structure of multiple detectors producing a measurable neural response. Hence, the suggested identification method is comprised of two consecutive stages addressing each of the above aspects. Furthermore, visual stimulus design for high spatial excitation order has been investigated.

The second topic is parameter estimation of mathematical model for testosterone regulation in the human male. The main challenges of this application are in the unavailability of input signal measurements and the presence of an unknown pulsatile feedback in the system resulting in a highly nonlinear closed-loop dynamics. Semi-blind identification method has been developed based on a recently proposed pulse-modulated model of pulsatile endocrine regulation.

The two system identification problems treated in the thesis bear some resemblance in the sense that both involve measured signals that can be seen as square-integrable functions of time. This property is handled by transforming the signals into the Laguerre domain, i.e. by equivalently representing the functions with their infinite Laguerre series.

Keywords: system identification, biomedical systems, insect vision, endocrine systems, orthogonal basis functions, time delay, impulse response, Laguerre functions, Laguerre polynomials, excitation design

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List of papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


III Alexander Medvedev and Egi Hidayat. Laguerre domain modeling of continuous time delay in the face of finite-dimensional perturbation. Submitted for possible publication.


V Egi Hidayat, Alexander Medvedev, and Karin Nordström. Identification of the elementary motion detector model in fly motion vision from intracellularly recorded neural data. Submitted for possible publication.


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1. Introduction

As the human race is eager to find a way to live better, healthier, and longer lives, the demand for mathematical modeling in life science is rapidly increasing. The possibility to explore biological phenomena by analyzing mathematical constructs, i.e. in silico, attracts and fascinates researchers in biology, medicine, applied mathematics as well as in various fields of engineering. Cooperative and interdisciplinary research has already led to the emergence of such scientific areas as bioengineering (biomedical engineering), bionics, or more general, biorobotics, computational neuroscience, and systems biology.

The term "systems biology" is defined by the European Science Foundation as the systematic study of complex interactions in biological systems, carried out primarily by methods from dynamical systems theory [34]. Generally, two focal points for the impact of practicing systems biology in medicine are identified: new insights in biology and novel intervention strategies derived from these insights [50]. The former goal can be achieved by mathematical modeling and model analysis combined with informative biological and clinical data. To meet the latter goal, systems biology has to be augmented with design tools because engineering an intervention strategy based on a mathematical model and a desired outcome is not straightforward. Citing H. Kitano in [30]: "Although the road ahead is long and winding, it leads to a future where biology and medicine are transformed into precision engineering".

To stimulate and support research at the intersection of life science and mathematics, massively funded and highly ambitious research programs have been undertaken on national and international levels. The most recent examples are the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) program in USA and the Human Brain Project, which is a new initiative launched by the European Commission as part of its Future and Emerging Technologies (FET) program.

Applications of system identification, generally defined as mathematical modeling from data, to biological systems confront a number of fundamental challenges. One of those is the natural variability of biological responses. In contrast with technical (engineered) systems, the response of a biological system to the same stimulus is seldom the same in different experiments. This is usually referred to as intra-individual variability in biomedical research. Another type of biological variability is the inter-individual one, meaning that the response differs between individuals of the same species. Furthermore, biological systems tend to exhibit high degree of nonlinearity. A constant input signal can result in a periodic response and vice versa, manifesting inherently nonlinear behavior of the system. Put in system-theoretical terms, the
nonlinear dynamics and non-stationarity of biological systems require large quantities of data for the estimation of both nominal behaviors and characterisation of the system-specific uncertainty (variability), which are very seldom available.

This thesis covers system identification approaches developed for applications within two biomedical fields: neuroscience and endocrinology.

Regarding the former topic, the thesis considers parameter estimation of the classical elementary motion detector (EMD) model [25] in insect vision. This mathematical construct is well-reputed and has been used for a long time in studies of motion detection. Nevertheless, formal parameter estimation techniques for the dynamics of the celebrated model hardly exists, while numerous modifications of the model structure have been suggested in the biological literature, in order to make it fit experimental data. The laboratory experimental setups allow stimulation of the eye of an insect to a practically unlimited variety of visual stimuli. However, it is currently not possible to measure the response of a single EMD to a stimulus as the biological circuitry implementing the EMD is not yet localized. The best available measurements pertaining to the EMD output are from a pooled output of multiple detectors wired in a certain spatial structure. Hence, a suitable identification method for such a system has to deal with a two-dimensional perspective, i.e. in time and space.

The second topic is parameter estimation of testosterone regulation in the human male. The situation with identification data availability in this research problem is opposite to that in insect vision. The system identification data are the output measurements in the form of hormone concentrations in blood serum. No input signal measurements can be obtained in the human for ethical reasons. Thus, the problem at hand is a so-called blind identification problem, where both the system dynamics and the input signal have to be estimated. To make it more challenging, the complete system involves an unknown pulsatile feedback resulting in a highly nonlinear closed-loop dynamics.

Completely distinct at first glance, the two system identification problems of this thesis are related to each other, both biologically and mathematically. The biological coupling is that the visual system and the control of the endocrine system are implemented using neurons and related to the brain. The mathematical relationship is established through the character of the signals used for system identification: they are decaying in time and belong to the class of functions integrable with square, i.e. $L_2$. In this work, this is handled by dealing with the involved signals in the Laguerre domain, i.e. via equivalently representing the functions by their infinite Laguerre series.
1.1 Thesis outline

This thesis is composed of two parts. The first part presents a comprehensive summary of the thesis work and the second part contains the actual papers that the thesis is based on.

The thesis outline is as follows. Chapter 2 presents an introduction to insect vision and, particularly, to the EMD model. A structure (layer) of multiple EMDs in the insect eye exhibits a two-dimensional (spatiotemporal) response. This leads to a two-stage identification algorithm, one stage for the estimation of the dynamics of an individual EMD and another for the spatial distribution of those. The experimental setup utilizing a Cathode-Ray-Tube (CRT) monitor for the visualization of stimuli introduces pulse modulation of the stimuli due to the refresh rate.

Chapter 3 presents an introduction to mathematical modeling and parameter estimation in endocrine systems. The well-studied and relatively simple system of testosterone regulation in the male is addressed to illustrate the proposed identification approach. The measured signal is the concentration of the luteinizing hormone that has pulsatile behavior and whose secretion is stimulated by an unmeasurable input, the concentration of a release hormone.

Chapter 4 provides a brief introduction to system identification in the Laguerre domain for systems with input and output signals in $\mathbb{L}_2$.

Chapter 5 contains a short summary of the included papers.

List of papers not included in the thesis

Following is the list of papers that are not included in the thesis but are relevant to the content of the thesis.

- E. Hidayat and A. Medvedev, Laguerre domain identification of continuous linear time delay systems from impulse response data, *IFAC World Congress*, Milano, Italy, September, 2011.
2. Parameter estimation of the Elementary Motion Detector model in the insect visual system

The visual system plays a very important role in the survival of many living organisms, on the ground, in the water, or in the sky, even if the visual system characteristics might differ for different species. A predator, such as an eagle, has very acute vision, allowing it to spot its prey from very far away. A rabbit, on the other hand, has a visual system with a reception field that covers a very wide area, to allow identification of approaching predators.

The visual system of insects, such as flies or bees, relies on the special compound eyes. Such eyes consist of many photoreceptors that see in slightly different directions. This spatially distributed structure provides a perceived image of a very wide-angle view.

![Compound eyes of a hoverfly](image)

*Figure 2.1. Compound eyes of a hoverfly*

The insect visual system has been studied for decades. One of the popular research topics is motion detection. Similar as other organisms, flying insects are able to track a trajectory while avoiding collision with stationary and mobile obstacles and simultaneously locating their target. Such advanced flight maneuver capabilities require high performance of data processing on a moderate complexity neural network with a very limited energy supply, and in real time. Being able to do such computation with a small brain, the visual system of an insect is very impressive and inspiring to an engineer. That is also one of the main reason that remarks the technological significance of motion vision research in insects.
In the research field of robotics, specifically in mobile robots, the compound eye systems are the most advanced ones when it comes to collision avoidance. A very wide visual receptive field combined with fast computation times are highly desirable in both ground and aerial robots.

Even though the peripheral visual systems are quite different in human and insects, there is general consensus that motion vision is coded in remarkably similar ways in the vertebrate visual cortex and the insect brain. It is mentioned that most animals with eyes compute local motion using fundamentally similar spatiotemporal correlation mechanisms [6]. Since insects are physiologically accessible and individual neurons readily identified during experimentation, they are attractive animal models for motion vision research.

There are several mathematical constructs describing local motion detection in visual systems, such as the elementary motion detector model (EMD) [25] and its modified versions, or the Volterra models [41]. This thesis presents an identification method for the classical EMD model that can however be modified to handle more sophisticated formulations.

2.1 Motion detection in insect vision

Biological visual systems are generally accepted to compute local motion via so-called elementary motion detectors (EMDs; for recent review, see [6]). The original model for the EMD was based on behavioral responses to grating patterns and flashing dots in the beetle, Chlorophanus [25]. Typically, a beetle was placed inside a spinning drum, and the optomotor response to different patterns moving at different velocities was recorded using a torque meter.

A similar underlying computational structure has since been confirmed in a range of animals, including flies, wallabies, and humans [11]. Importantly, whereas the EMD can explain many biological observations, its neural components still remain elusive. In the fly optic ganglia, lobula plate tangential cells (LPTCs) are believed to spatially pool the output from many EMDs [19]. The physiology of LPTCs, and the behavioral output of insects, closely match the predictions of the EMD [5]. It is, however, important to note that no one has been able to record from the EMD itself. In biological visual systems, one can measure from the photoreceptors [40], which provide the input to the EMD, and the spatially pooled output [26], but not the response of the EMDs themselves. The evidence is thus indirect.

In the classical EMD model, the luminance change from two neighboring photoreceptors are correlated after filtering or delaying the input from one [7]. By subtracting the output from a mirror symmetric unit, direction opponency is achieved. The spatial sampling of the EMD is based on the ommatidial mosaic of the eye, where the optics sets the limit. Since different insects have different spatial acuity [31], they show corresponding variations in spatial frequency optimum [39]. The higher spatial resolution in the vertebrate retina,
Figure 2.2. Sections of the fly eye. The input of EMD is located in the retina while the output is located in the lobula plate.

subsequently gives peak sensitivity to even higher spatial frequencies [15]. Using ingenious experiments with a focused light source that could selectively stimulate single photoreceptors, it was shown that the spatial correlation takes place between nearest neighbors [19], and not next-nearest neighbors.

The delay is usually approximated by a low-pass filter [14, 22], but many variations to this have been presented over the years. Sometimes a high-pass filter is added to one or both of the inputs, before or after the low-pass filter [23, 8]. The low-pass filter usually has a time constant of 10-30 ms [24], which generates peak sensitivity to the type of temporal frequencies measured in steady-state LPTC [42] and behavioral responses [45]. Whereas the low-pass filter is usually described as a fixed modality, some authors suggest that the time constant adapts to continuous motion stimulation [4].

Using more modern genetic tools in the model organism Drosophila, the cellular components of the EMD are slowly starting to be unraveled [20], but with each step forward a new controversy arises, such as whether ON and OFF contrast changes are processed separately [28] or not [10]. Furthermore, there are several physiological and behavioral observations that cannot be explained using the EMD. For example, flies and humans readily perceive higher-order motion [32, 47] and reverse phi motion [48], even if these are supposed to generate paradoxical motion cues in an EMD [55]. Another intriguing contradiction is the observations that even if the EMD is highly dependent on contrast and spatial frequency [8], and the biological responses behave as predicted when using single frequency images [15], the responses to natural scenes seem to code velocity consistently across a broad range of image contrasts [2].
2.2 Mathematical model of EMD

The EMD model [25] (Fig. 2.3) can be summarized in mathematical terms as follows:

\[
\begin{align*}
    v^+(t) &= \int_0^t w^+(t - \theta)u^+(\theta) \, d\theta, \\
    v^-(t) &= \int_0^t w^-(t - \theta)u^-(\theta) \, d\theta, \quad (2.1) \\
    y(t) &= v^+u^- - v^-u^+,
\end{align*}
\]

where \(u^+\) and \(u^-\) are the scalar inputs of the EMD, \(y\) is the output, and \(w^+\) and \(w^-\) are the impulse responses of the low-pass filters in the input channels. Both \(w^+\) and \(w^-\) are assumed to be finite-dimensional, to simplify calculations. The involved time delays are expected to be closely approximated by finite-dimensional dynamics via Padé or Laguerre expansions [21, 37] and incorporated in \(w^+\) and \(w^-\).

Figure 2.3. The basic nonlinear EMD model.

In the earlier study of EMD, the dynamics of the two channels \(w^+\) and \(w^-\) are considered identical. This construction is usually called symmetrical EMD structure. With this assumption, the solution for the output signal \(y(t)\) in (2.1) is easier to obtain. However, such a simplification results in a model missing some properties of the response. For example, consider a sine grating stimulus, which is quite common in studies of the fly visual system. With the symmetrical structure of the EMD, the steady-state solution lacks the periodic component at double frequency of the input that appears due to the product in the output mapping of the EMD model, even though the corresponding periodic behavior is visible in the measured laboratory data. Figure 2.4 shows an example of spectrum analysis of the response of an LPTC to a sinusoidal grating stimulus with temporal frequency of 30 Hz. The significant peaks at the stimulus frequency and its doubled frequency can be interpreted as periodic behavior of the response at these frequencies. More recent research tends to allow for non-symmetrical dynamics in the EMD and thus improve the fidelity of the model [23, 8].
Figure 2.4. Spectrum analysis of the response of an LPTC to a sinusoidal grating stimulus with temporal frequency of 30 Hz. The spectrum of output signal at the input frequency and its doubled frequency are marked. The refresh rate of the CRT monitor is 160 Hz.

2.3 Experimental setup

A classical experimental setup for studying the visual system of a fly is presented in Fig. 2.5.(a). The machinery consists of a rotating drum with the stimulus pattern. The motion speed of the stimulus is controlled by the torque given to the drum. If the drum rotates clockwise, the insect will generate a yaw torque in the clockwise direction, and vice versa [45]. The most common pattern used in the classical setup is the grating pattern.

Figure 2.5. Experimental setup for insect vision studies.
Nowadays, the stimuli are generated using computers on display screen as seen in Fig. 2.5.(b). The typical screens used in the experiments are high-end CRT monitors that provide high refresh rate, but at the expense of spatial resolution.

By using the modern setup with high-end graphic cards, it is possible to generate a large range of stimuli. Nevertheless, the most used stimuli in insect vision studies are the sinusoidal grating stimuli.

![Graph showing input and output signal forms.](image)

Figure 2.6. Input and output signal forms. Upper plot: Photodiode measurement of sinusoidal grating (20 Hz, wavelength 50 pixels) displayed on a 160 Hz CRT monitor. Lower plot: Example intracellular response of an HS (horizontal system, an LPTC) neuron in the left lobula plate of the fly.

Being able to reproduce stimuli with good image quality, the CRT monitor refreshes the screen at a certain frequency. The refresh rate, up to 200 Hz, introduces modulation to the original stimulus signal form. The resulting modulated signal appears as a sequence of pulses as shown in the upper plot of Fig. 2.6. The lower plot shows the response of an LPTC neuron to the modulated signal. The pulsatile high frequency component that is visible throughout the measured data corresponds to the refresh rate of the monitor.

It can be seen in the data that each pulse of the modulated stimulus evokes a corresponding pulse response in the neuron. Thus, both pulses can be thought of as signals that belong to $L_2$, i.e. to the space of square-integrable functions. In this class of signals identification in Laguerre domain is suitable, which technique is discussed further in Chapter 4.
2.4 Spatial excitation of the stimulus

As mentioned earlier, the LPTC response is believed to be the spatially-pooled output of multiple local EMDs wired in a certain structure and creating an EMD-layer. A simple way to model the relationship between the input to the photoreceptors, the local EMDs, and the LPTC neuron is given by the diagram in Fig 2.7.

![Diagram of EMD-layer structure](image)

**Figure 2.7. EMD-layer structure**

The dynamics of all the connected EMDs are believed to be similar. However, each particular EMD contributes to the overall output signal via a static gain, i.e. a weight. This model can be described by the following expression

\[
y(t) = \sum_{i=1}^{N} g_i y(t, i) \tag{2.2}
\]

where \(y(t, i)\) represents the output of the \(i\)-th EMD, \(g_i\) is the weight of the \(i\)-th EMD, and \(y(t)\) as the EMD-layer output. In this formulation, it is assumed that the layer comprises \(N\) local detectors. Hundreds of EMDs are expected to contribute to an experimentally measurable neural response [7].

The expression for the output of EMD-layer in (2.2) is derived based on the assumption that there are \(N\) spatially distributed contributing EMDs in the layer. Clearly, two EMDs receiving the same input cannot be distinguished since they possess identical dynamics.

In order to obtain a unique solution for \(N\) unknowns, at least \(N\) linearly independent equations are required. The excitation order of the stimulus in terms of spatial distribution plays an important role in preventing the linear dependency between the individual EMD outputs. In the concept of persistent excitation of an input signal in system identification literature [43], the excita-
tion of a signal comprised of sinusoidal waves can be increased by introducing more frequency components within the signal.

2.5 Variability of the response with respect to temporal excitation of the stimulus

Referring to [54], the neuron response of a fly will have less variance for a stimulus with a higher excitation order. This conjecture is essential in the stimulus design for biological vision studies. Thus, experiments were performed with visual stimuli corresponding to input signals of different excitation order. For each type of stimulus, the experiments were conducted for 5 trials each lasts for 2 s with sampling frequency of 10 kHz. As the lowest stimulus frequency is 5 Hz, the period of observation is chosen as 0.2 ms. The mean and the variance of signal within one period of observation is computed based on Gaussian distribution. It is shown in Fig. 2.8 and 2.9 that the variance of the neuron response is considerable lower for higher excitation order stimulus. The result agrees well with the statement given in the beginning of this section. This result shall promote the importance of higher excitation order of the stimulus in insect visual system study.

![Figure 2.8](image)

(a) Sine grating 5 Hz  
(b) Sum of sine waves grating

*Figure 2.8.* Confidence interval comparison based on Gaussian distribution computed at each sampling point. The grey areas represent the confidence region. The solid lines depict the mean values.
Figure 2.9. Standard deviation comparison between different types of stimuli. For single-tone stimuli, higher frequency results in lower standard deviation. The neural response to the Tri-freq signal (sum of three sinusoidal waves [5, 20, 40] Hz) has the lowest standard deviation that as well corresponds to the lowest variance.
3. Identification of testosterone regulation system

One of the subsystems of the human body is the endocrine system. The endocrine system works together with the other subsystems of the organism in supporting and maintaining such basic functions as reproduction, growth, etc [16]. The endocrine system is based on glands that are distributed all over the human body. Endocrine glands produce signal substances - hormones that communicate information between cells and, thus, also organs. Hormones travel with blood flow from one organ to another transmitting information coded in the hormone concentration and also in the way how that concentration varies in time. Once secreted, the hormone molecules can be stored in the gland until they are requested to be released into blood.

The secretion of hormones by endocrine glands into the blood stream occurs in continuous (basal) or pulsatile (non-basal) manner. As stressed in [52], pulsatility is now recognized as a fundamental property of the majority of hormone secretion patterns. The term pulsatile generally refers to a sudden burst occurring in the face of a relatively steady baseline process.

3.1 Testosterone regulation system

One of the highly influential pulsatile endocrine systems in the human body is that of testosterone regulation [51]. Testosterone is secreted primarily in testes of males and ovaries of females. Small amount of testosterone is also secreted by the adrenal glands. For men especially, testosterone plays a very important role in many aspects such as sperm production, growth of muscle, bones, and fat tissue.

The testosterone regulation system involves mainly two other hormones, i.e. luteinizing hormone (LH) and gonadotropin-releasing hormone (GnRH). These two hormones are secreted inside human brain, in different parts of it, namely hypophysis and hypothalamus. Secretion of GnRH stimulates the secretion of LH, then the concentration of LH stimulates the secretion of testosterone. Testosterone, on the other hand, inhibits the secretion of GnRH. Thus a negative endocrine feedback is implemented. It is also obvious that time delay is an essential phenomenon in the closed-loop regulation of testosterone due to the transportation route that the hormones need to travel from the brain to the testes and back. It also takes time for a gland to produce a releasable pool of a hormone when it is not readily available.
3.2 Convolution model

At present, the most prominent technique to analyze the dynamic hormone regulation from hormone concentration data is based on the deconvolution approach. Given the measurements of hormone concentration $C(t)$ with initial condition $C(0)$ together with prior information of the elimination rate profile $E(t)$, one could obtain the secretion rate $S(t)$ by solving the deconvolution problem from the following relation

$$C(t) = \int_0^t S(\tau)E(t - \tau)d\tau + C(0)E(t).$$

In [13], a comparison of several deconvolution approaches are presented, e.g. Least squares (LS) deconvolution, Maximum A Posteriori (MAP) deconvolution [12], and Wiener deconvolution.

The degree of a priori information about the hormone secretion profile $S(t)$ defines the difficulty in solving the deconvolution problem. When no information is available, the process is called blind deconvolution and would rather be considered as an ill-conditioned problem. In most cases, the secretion profile is assumed to follow a certain dynamic pattern, which renders an easier problem and is called model-based deconvolution. There are many algorithms for
Figure 3.2. Reconvolution of LH concentration from 20-hours measurement.

Figure 3.3. Reconvolution of LH concentration from one major pulse by means of three deconvolution methods. Notice that two of the methods neglect the possible existence of a secondary pulse that produces second peak at around 70 minutes mark.

hormone secretion analysis based on the deconvolution methods, e.g. WEN Deconvolution [13], WINSTODEC [44], AutoDecon [29].

When a train of pulses from 20 hours of LH measurements is being analyzed, most deconvolution-based methods could, generally speaking, capture the major pulsatile secretion, as seen on Fig. 3.2. However, they would also tend to neglect the existence of secondary pulses in between the major pulses, see Fig. 3.3. Thus, when one wants to perform deep analysis of a single secretion pulse, a different approach is needed.
3.3 Smith model

The underlying dynamics of testosterone (Te) regulation in the male can be described by the following equations

\[
\begin{align*}
\dot{R} &= f(T) - B_1(R), \\
\dot{L} &= G_1(R) - B_2(L), \\
\dot{T} &= G_2(L) - B_3(T).
\end{align*}
\] (3.1)

This model is known as the Smith model and represents, in a highly simplified manner, the regulation in the axis GnRH-LH-Te. The state variables correspond to the hormone concentrations: \(R\) of GnRH, \(L\) of LH and \(T\) of Te. The non-negative functions \(B_1, B_2, B_3\) representing hormone clearing and \(G_1, G_2\) representing secretion usually accept linear approximation. In the original formulation of the model, the secretion function \(f(\cdot)\) is continuous and does not reflect the pulsatile character of the feedback regulation in question.

To model the episodic secretion of GnRH in response to changes in Te, the Smith model is complemented by a pulse-modulated feedback in [9]. This leads to a simplified form of the model

\[
\dot{x} = Ax + B\xi(t), \quad y =Cx
\] (3.2)

with

\[
\begin{align*}
A &= \begin{bmatrix} -b_1 & 0 & 0 \\ g_1 & -b_2 & 0 \\ 0 & g_2 & -b_3 \end{bmatrix}, \quad B = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}, \quad C = \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}^T, \quad x = \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}
\end{align*}
\] (3.3)

where \(b_1, b_2, b_3, g_1,\) and \(g_2\) are positive, and \(x_1 = R(t), x_2 = L(t), x_3 = T(t)\). The pulsatile secretion is represented by a sequence of Dirac delta functions as input signal, based on the reasoning that the delta functions mark the pulse firing time but do not model the actual secretion profiles

\[
\xi(t) = \sum_{n=0}^{\infty} \lambda_n \delta(t - t_n).
\] (3.4)

3.4 Bipartite endocrine model

The main concern of this study is to estimate the relationship between pulsatile secretion of GnRH and LH concentration level. Thus, model (3.2) is simplified further to the second-order dynamics expressed by

\[
A = \begin{bmatrix} -b_1 & 0 \\ g_1 & -b_2 \end{bmatrix}, \quad B = \begin{bmatrix} 1 \\ 0 \end{bmatrix}, \quad C = \begin{bmatrix} 0 \\ 1 \end{bmatrix}^T, \quad x = \begin{bmatrix} R(t) \\ L(t) \end{bmatrix}.
\] (3.5)
A GnRH concentration pulse is given by the response of a stable first-order system with the time constant $1/b_1$ to a Dirac delta-function fired at time $t_k$ and with the weight $\lambda_k$.

From the measured data, it is seen that the majority of the released LH concentration pulses have at least one minor pulse that follows a major one. This leads to a specialized parameter estimation problem with one primary and one secondary GnRH pulsatile release and corresponds to a well-studied case of 2-cycle detailed in [9] with the input sequence

$$\xi(t) = \delta(t) + \lambda \delta(t - \tau)$$

and parametrized in only two additional parameters, the ratio $\lambda$ and the delay $\tau$ between the secondary and primary impulses.

Based on the original model in (3.2), with state space matrices (3.5) and input signal (3.6), the model of LH concentration profile is given by

$$L(t) = \frac{g_1}{b_2 - b_1} (e^{-b_1 t} - e^{-b_2 t}), \quad 0 \leq t < \tau,$$

$$L(t) = \frac{g_1}{b_2 - b_1} (\eta(b_1)e^{-b_1 t} - \eta(b_2)e^{-b_2 t}), \quad \eta(b_i) = 1 + \lambda e^{b_i \tau}, \quad \tau \leq t < T,$$

with $T$ representing the least period of the closed-loop system solution. This model involves nonlinearity that makes any direct implementation of classical linear identification methods inapplicable.

This thesis presents two ways of estimating the model parameters of hormone pulsatile regulation system. The first approach is based on weighted nonlinear least-squares method. The second approach employs system identification in terms of Laguerre functions [35],[36],[53]. The first approach is briefly presented in the following section, while the second approach is given in Chapter 4.

### 3.5 Least-squares method

When it comes to fitting data to a given function, least-squares method is the most celebrated approach that has been used in many years and zillions of applications, [33], [43]. Not only because the idea behind it is simple and reasonable, but also because the result it gives is in many cases quite good. Numerous advanced identification algorithms have been developed departing from the least-squares method. Several reasons why least-squares method is so popular are suggested in [1]. The first reason is that most estimation problems can be embedded in this framework. Second, it is very tractable. Then, there are plenty of mathematical tools and algorithms available since it has been studied for such a long time.
Based on this motivation, it is interesting to see how well the least-squares method will perform in solving the estimation problem described in the previous section. The underlying model is simple enough and the available data are time series, which makes it a perfect framework for implementing the least-squares method. Even though the least-squares method is suitable to solve the problem in estimating (fitting the data to) the model given in (3.7), there are some adjustments that have to be implemented to satisfy the model properties. First, instead of the ordinary least squares, it has to be a nonlinear least-squares method since the underlying model is nonlinear. The latter also means that analytical calculation of the optimal estimate is not possible. Thus, numerical search is the only way to solve the minimization problem. Second, the data have to be handled so that some measured instances will have higher priority to be fitted that the others, which property can be achieved by introducing weights in the least-squares method. Finally, to make biological sense, the parameter estimates have to fulfill certain conditions. This hints to the use of a constrained least-squares method.

As it has been mentioned in the previous section, this study focuses on parameter estimation problem with one primary and one secondary GnRH pulsatile release with the input sequence given in (3.6). Fig. 3.4 shows three examples of LH concentration profile that exhibits a secondary GnRH pulsatile release.

![Figure 3.4](image_url)

*Figure 3.4.* Three pulsatile profiles of LH concentration measured in human males. Notice that all the pulses exhibit first a primary and then a secondary GnRH release event approximately at the same time. The hormone profiles are synchronized with respect to primary release.
The first condition that has to be fulfilled is the timing of primary pulse peak given by

\[ t_{\text{max}} = \frac{\ln(b_1) - \ln(b_2)}{b_1 - b_2}. \]

Another condition is defined for the maximum concentration for the primary pulse

\[ L_{\text{max}} = \frac{g_1}{b_2 - b_1} \left( e^{-b_1 t_{\text{max}}} - e^{-b_2 t_{\text{max}}} \right). \]

Satisfying these conditions would lead the optimization to the intended result.
4. System identification based on Laguerre functions

A popular approach to system identification in systems whose input and output signals are $L_2$ functions is by considering the measured signals in a basis of orthonormal functions [49]. When the problem in hand has a known parametrized structure, this approach can be quite successful.

Within the orthonormal basis approach, the time-domain measurements of the input and output signals (and the system representation) are equivalently transformed to a different domain defined by the basis functions. Naturally, all system properties are preserved. However, by selecting a particular basis, some properties can be emphasized while the influence of other factors can be downplayed. Orthonormal basis functions have also often found a fair share of applications in the area of signal processing. Nevertheless, numerical tools of identification and signal processing in orthonormal bases are not well-developed. Most methods involve numerical schemes of continuous integration that are prone to numerical issues for signals produced by higher-order dynamics.

One family of orthonormal rational functions that is widely used in the system identification area is the Laguerre functions. A Laguerre function is an exponential function in time domain and will converge to zero as the argument goes to infinity, see Fig. 4.2. This property suits really well in approximation of a stable impulse response as it is shown on Fig. 4.4.

Laguerre functions $l_k(t)$, $k = \{0, \infty\}$, yield an orthonormal basis in $L_2$. The Laguerre function of order $k$ is defined as

$$l_k(t) = \sqrt{2\alpha} e^{-\alpha t} L_k(2\alpha t),$$

with $\alpha > 0$ is the Laguerre parameter, $k$ is a positive number, and Laguerre polynomial $L_k(2\alpha t)$ is given by

$$L_k(\zeta) = \sum_{n=0}^{k} \binom{k}{n} \frac{(-\zeta)^n}{n!},$$

where $\zeta = 2\alpha t$. The Laplace transform of $k$-th continuous Laguerre function is given by

$$\ell_k(s) = \frac{\sqrt{2\alpha}}{s + \alpha} \left(\frac{s - \alpha}{s + \alpha}\right)^k.$$
In terms of the Laguerre shift operator $T(s)$ and a normalizing function $\tilde{T}(s)$, one has $\ell_k(s) = \tilde{T} T^k$, where

$$T(s) = \frac{s - \alpha}{s + \alpha}; \quad \tilde{T} = \frac{1}{\sqrt{2\alpha}} (1 - T(s)) = \frac{\sqrt{2\alpha}}{s + \alpha}.$$  

The Laguerre spectrum element $y_k$ characterizes the contribution from Laguerre function $l_k(t)$ in the true signal $y(t) \in L_2$. This term is also called the Laguerre coefficient and evaluated as a projection of $Y(s)$ onto $\ell_k(s)$

$$y_k = \langle Y, \ell_k \rangle,$$

with $k \in \{0, \infty\}$. The inner product is defined as

$$\langle Y, \ell_k \rangle = \frac{1}{2\pi j} \int_{-j\infty}^{j\infty} Y(s) \ell_k(-s) \, ds.$$  \hspace{1cm} (4.1)

According to Riemann-Lebesgue lemma, the integral over an infinite half arc $\Gamma_2$ in Fig. 4.1 is

$$\frac{1}{2\pi j} \int_{\Gamma_2} Y(s) \ell_k(-s) \, ds = 0,$$

and line integral in (4.1) can be conveniently evaluated as a contour integral

$$\langle W, \ell_k \rangle = \frac{1}{2\pi j} \oint_{\Gamma} Y(s) \ell_k(-s) \, ds,$$  \hspace{1cm} (4.2)

over a clockwise contour on the whole right half part of complex plane $\Gamma$.

![Figure 4.1. Contour for inner product evaluation.](image)

The Laguerre spectrum depends on the value of Laguerre parameter $\alpha$ that is used to form the Laguerre functions. Fig. 4.3 and Fig. 4.4 show how two Laguerre spectra with different Laguerre parameter values approximate a true signal. It is apparent that one of the representations captures the actual signal better with the same number of the basis functions. Notice that infinite number of Laguerre functions is needed in order to obtain a perfect approximation of the true signal.

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Figure 4.2. Representation of Laguerre functions of different order in time domain with Laguerre parameter $\alpha = 0.1$.

Figure 4.3. Two different Laguerre spectra produced from one signal by using two different Laguerre parameter values.
Generally speaking, there are two approaches available to utilize Laguerre functions in system identification. The first approach involves computing an approximation of the Laguerre spectra of the input and output signals [17], [18]. The other one rather describes the system dynamics in Laguerre domain [3], [27], [38], [46], [49]. Clearly, the former approach is limited to the identification problems where the input and output information is represented by $L_2$ functions. The benefit is that no approximation of the system dynamics is involved. Further, the classical identification tools have theoretically guaranteed performance under sufficient (temporal) excitation order of the input, which is not the case for $L_2$ signals. The latter approach imposes no limitation on the type of the input and output signals but approximates the system dynamics with a truncated series of Laguerre functions. An extra step is implemented to recover the parameters of the underlying system in the time (or Laplace) domain.

4.1 Finite-dimensional dynamics in Laguerre domain

Consider the continuous time-invariant system

\[
\dot{x}(t) = Ax(t) + Bu(t), \quad (4.3)
\]

\[
y(t) = Cx(t),
\]

where $A, B, C$ are constant real matrices of suitable dimensions. The matrix $A$ is assumed to be (Hurwitz) stable and the initial conditions on (4.3) are
\( x(0) = x_0 \) and \( u(\theta) \equiv 0, \theta \leq 0 \). Assume that the Laguerre parameter \( \alpha \) does not belong to the spectrum of \( A \), i.e. \( \det(\alpha I - A) \neq 0 \). From this point on, the resolvent matrix of \( A \) is denoted as

\[
R_A(s) = (sI - A)^{-1}.
\]

Let \( U_k \) and \( Y_k \) be the vectors of Laguerre coefficients of the input and output signals, respectively, i.e.

\[
U_k = \begin{bmatrix} u_0 & \ldots & u_k \end{bmatrix}^T, Y_k = \begin{bmatrix} y_0 & \ldots & y_k \end{bmatrix}^T.
\]

For system (4.3), the following relationships hold between the Laguerre coefficients of the input and those of the output:

\[
Y_k = \Gamma_k x_0 + \Theta_k U_k,
\]

where

\[
\Gamma_k = \begin{bmatrix} H & \cdots & \cdots & \cdots \\ HF & \cdots & \cdots & \cdots \\ \vdots & \cdots & \cdots & \cdots \\ HF^k & \cdots & \cdots & \cdots \end{bmatrix}, \quad \Theta_k = \begin{bmatrix} J & 0 & \cdots & 0 \\ HG & J & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ HF^{k-1}G & HF^{k-2}G & \cdots & J \end{bmatrix},
\]

and the Laguerre domain system matrices \( F, G, H \) are defined in Table 4.1, [17].

**Table 4.1. System matrices in Laguerre domain.**

<table>
<thead>
<tr>
<th></th>
<th>( T(A) )</th>
<th>( -T(A)B )</th>
<th>( C(T(A)) )</th>
<th>( C(\alpha I - A)^{-1}B )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>F</strong></td>
<td>( F )</td>
<td>( G )</td>
<td>( H )</td>
<td>( J )</td>
</tr>
</tbody>
</table>

In a convolution form, the above result reads:

\[
y_k = \sum_{i=0}^{k-1} HF^{k-1-i}Gu_i + Ju_k.
\]

With a single impulse as input, \( u_i = \sqrt{2} \alpha, \ i = [0, k] \) and

\[
y_k = \sum_{i=0}^{k-1} \sqrt{2} \alpha (-2 \alpha) (-1)^i CR_A^i + 2(\alpha)(pI + A)^i B
\]

\[+
\sqrt{2} \alpha CR_A(\alpha)B. \tag{4.4}\]
It should be noted that for impulse response without input delay, the Laguerre coefficients of the output signal can also be derived by calculating the linear integral of the scalar product via counter-clockwise contour integration over the left-half plane of the complex plane, namely $\Gamma_c$ in Fig. 4.1. This procedure actually produces a result equivalent to (4.4) but with a much simpler expression

$$y_k = (-1)^k \sqrt{2\alpha CR_A^{k+1}} (\alpha)(\alpha I + A)^kB.$$  (4.5)
5. Summary of papers

Paper I
This paper contributes a general representation of the impulse response of a continuous linear time-delay system in terms of Laguerre functions. This representation is then used to develop an algorithm for continuous time-delay system identification combining subspace identification with time-delay gridding.

Paper II
The implementation of parameter estimation methods for a pulsatile endocrine model is discussed. Two methods are dealt with, i.e. the weighted nonlinear constrained least squares method and Laguerre functions-based method. Numerical issues with the method in Paper I are discussed and addressed to achieve better performance.

Paper III
A formal proof of an algorithm for pure time-delay estimation based on Laguerre functions is given and its robustness against finite-dimensional perturbation is investigated. It is shown that in theory it is possible to completely remove the effect of finite-dimensional perturbation dynamics in the case of pure time-delay estimation by selecting a certain value of the Laguerre parameter.

Paper IV
A typical neural response data set in fly visual system study contains sequence of pulses due to the refresh rate of the monitor. This motivates parameter estimation based on orthogonal functions such as Laguerre functions. The main contribution of this paper is a description of the classical EMD model in terms of Laguerre spectra of the input and output. It is shown that the transformation to the Laguerre domain preserves the basic skew-symmetric properties of the original model that is a Wiener system. Exploiting the properties of the product of two Laguerre spectra, the problem can be recast as a linear one.
Paper V
In this paper, the identification approach presented in Paper IV is implemented on laboratory data. The measured neural response from an LPTC is regarded as the pooled output of an EMD layer modeled by a linear combination of spatially separated EMDs. The identification procedure thus includes estimation of the contribution of each EMD in the layer parametrized by a weight. Two stages of identification are required to obtain a complete layer model. The first step is parameter estimation of the individual detector based on the method presented in Paper IV. The second step is the identification of the EMD weights based on a sparse estimation approach.

Paper VI
A layered structure of EMDs, whose output is measured at an LPTC, is expected to contain hundreds of spatially distributed detectors possessing highly similar dynamics. To distinguish between two EMDs, the input signals given to those have to be different. In this paper, spatial excitation properties of visual stimuli are studied. The main focus is on the sine grating type of stimuli. It is demonstrated that introducing a sum-of-sine waves grating as stimuli leads to more accurate estimates of the EMDs’ weight values.
6. Sammanfattning på svenska

Systemidentifiering spelar idag en viktig roll inom biologi som ett verktyg för empirisk matematisk modellering och individualisering av modeller. En grundläggande utmaning för identifiering av biologiska system är den variation som erhålls i systemsvar vid upprepade experiment under samma experimentförhållanden. I kontrast till tekniska, ingenjörsmässigt konstruerade system, så är svaret från ett biologiskt system till ett givet stimulus sällan det-samma. Detta refereras vanligen till som intra-individuell variation. En annan typ av biologisk variation är inter-individuell variation, vilket syftar på att svaret varierar mellan olika individer av samma art.

Biologiska system tenderar även att uppvisa en hög grad av olinjäritet. En konstant insignal kan t ex resultera i en periodisk systemrespons och vise versa, vilket är en manifestation för olinjära beteenden hos systemet. Uttryckt i systemteoretiska termer, den olinjära dynamiken och icke-stationariteten hos biologiska system kräver stora mängder data för skattning av både nominella beteenden och karaktärisering av den systemspecifika osäkerheten (variationen), vilket sällan är tillgängligt i praktiken.

Denna avhandling beskriver tillvägagångssätt för systemidentifiering, utvecklade primärt för applikationer inom två områden: neurovetenskap och endokrinologi.

Gällande det första området, så studeras parameterskattning för den klassiska "Elementary Motion Detector" (EMD)-modellen framtagen av Hassenstein och Reichardt 1956, för att matematiskt beskriva principerna för insektsseende. Denna matematiska modell är välrenommerad och har använts en längre tid för studier av rörelsedetektion. Ett antal modifieringar av modellstrukturen har föreslagits, i den biologiska litteraturen, i försök att anpassa modellen till experimentell data. Dock saknas, i stor utsträckning, formella metoder för parameterskattning, även för den enklaste EMD-modellen.

Den använda experimentuppsättningen för att stimulera insektens öga tillåter praktiskt taget obegränsad variation av visuella stimuli. Det är dock, i nuläget, inte möjligt att mäta svaret från en enskild EMD då den biologiska krets som implementeras EMD inte ännu har lokaliserats. De bästa tillgängliga mätningarna med avseende på EMD-utsignalen kommer från en grupp av multipla detektorer kopplade enligt ett specifikt spatialt schema. En lämplig identifieringsmetod måste således, för ett sådant system, operera i ett tvådimensionellt perspektiv, d.v.s. i tid och rum.

Det andra ämnet som behandlas i avhandlingen är parameterskattning i en modell för testosteronreglering i den manliga människokroppen. I detta fall så

Vid en första anblick, så kan dessa två systemidentifieringsproblem se helt skilda ut, men vid en närmare titt så är de besläktade, både matematiskt och biologiskt. Den biologiska kopplingen är att det visuella systemet och testosteronregleringen verkställs genom neuroner i en hjärna. Den matematiska kopplingen stammar från karaktären för de signaler som används vid systemidentifieringen: de är avtagande i tid och hör till klassen av kvadratiskt inte-integrerbara funktioner. Detta hanteras genom att studera de ingående signalerna i Laguerre-domän, d.v.s. att beräkna ekivalenta representationer av funktionerna genom oändliga Laguerre-utvecklingar.
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