

Polynomial Approximation of Time Series of Pupil Response to Controlled Light Stimuli

José Gerardo Cárdenas Solís¹, David Asael Gutiérrez Hernández^{1,*}, Edgar Guevara²,
R. Santiago-Montero¹, María Trinidad Galván González¹, Sergio Uribe López¹,
Rossana Rodríguez Montero¹, J. M. Carpio¹

¹Tecnológico Nacional de México, Instituto Tecnológico de León, División de Estudios de Posgrado e Investigación, León, Guanajuato, México

²CONACYT- Universidad Autónoma de San Luis Potosí, Coordinación para la Innovación y Aplicación de la Ciencia y la Tecnología, San Luis Potosí, S.L.P., México

Abstract In this paper we present an analysis of data coming from a biological effect in a human body. The pupil reflex, as a reaction of a well-controlled light stimulus, is recorded with a digital camera configured to 30 frames per second. Once the video is recorded; each frame is analysed, in order to register the diameter evolution with respect to the corresponding time of the taken frame. A vector of diameter changes and a vector of time are obtained. The correspondence between such vectors is plotted to identify the diameter behaviour along time. For this experiment, there were considered 6 individuals and two measurements for each one, one of them before breakfast and the other measurement 30 minutes after breakfast. Results indicate that, by means of computational ways, it is easy to mathematically characteristic a biological time series for a later reproduction for modelling purposes.

Keywords Pupil reflex, Biological time series, Mathematical approximation

1. Introduction

The pupil's response to light (dilatation and constriction) is controlled by the Ciliospinal center and the Edinger-Westphal nucleus, both branches of the Autonomous Nervous System (ANS). In a controlled environment with well-controlled and constant visual and luminous stimulus variables, the pupil may exhibit a random behaviour and this behaviour reflects the action of ANS [1], so the absence of response in pupil constriction to light indicate an afferent neuronal defect [2, 3].

Pupillometry is a non-invasive, low cost and fast technique. It has been applied, for example, in the monitoring of the central cholinergic system [2]. Pupillometry consists in measuring the pupil's size and its behaviour. In previous investigations, according to references [4, 5]. The pupil, previously dilated, is stimulated by means of a single pulse of light to obtain a graph representing the behavior of the pupil upon contraction. Due to the characteristics of the camera, a four-parameter sigmoid profile curves adjustment is performed, which are accumulated in a database to later use this data to describe

pupil behavior in people with diabetes [4] and Distinguish between clinically healthy and overweight groups of people, this, with the support of the k-means clustered.

Thus, our interest in the short term is to be able to characterize groups of people with different characteristics between them and thus identify, for example, pathologies, neurological problems, physiological states, among others, by means of a reliable technique that allows us to parameterize Biological signals and extract information that helps us to reproduce or model mathematically a biological signal or biological time series of non-linear behavior, coming from different destinations.

The study and analysis of time series is an important activity done in many scientific disciplines, like engineering, natural and biological sciences and industry. Generally, a characteristic that all the time series have on common is the high correlation between all the data points contented on them. This characteristic makes the difference between the kind of data under analysis. So, in this way, time series can be subjected to many mathematical and computational treatments like regression, trend seasonality and forecasting analyses that can be used to identify important factors or information that can represent a specific performance or a particular system or a special pattern that could exists within the data [6].

The principal interest behind the time domain approach is based on the correlations and dependencies between the

* Corresponding author:

david.gutierrez@itleon.edu.mx (David Asael Gutiérrez Hernández)

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data points of the event, experiment or test under study in a time series. Techniques of time domain analysis use data points as parametric functions in order to get a mathematical or computational model of the system [7] that can be furthered repeatable for different purposes or applications.

In biological time series, the correlation between data and time is not always a simple signal to be analysed. Working with the human world of non-linear, non-periodical and no repeatable signals that the brain generates for any stimulus over the human body is a complex research that gives new information every day. This new information might then be used for expanding the acquired knowledge and understand, by this way, different topics in different fields of science.

Biological time series data, by themselves, contain more information than data coming from well-controlled systems where an expected result is already predicted by different ways. Biological time series data cannot necessarily be evaluated with the commonly used methods of time series analysis, like autocorrelation and frequency domain techniques [8], instead, biological data are very sparse. Indeed, many time series consist of maybe a dozen quantities, measured at a handful of time points, and replicates are usually scarce [9]. This paucity of data, accompanied by minimal redundancy, immediately creates statistical challenges that have not been addressed in a systematic model of data treatment or in a specific way of computationally manipulation of biological data that can be always applied as a recipe that can always be followed.

In this paper, we propose a methodology to extract information from the pupil reflex for future applications on medical diagnoses. This methodology requires of a combination of mathematical and statistical processes together to a computational analysis of the data to get an understandable meaning of the biological time series for researching purposes, in other words, we propose a method of extracting information from biological signals or time series that consists of the mathematical approximation of the signal to a polynomial function, which allows us to understand the signal acquisition, model and treat it mathematically for the purposes which our research suggests by performing actual tests on human bodies. The signals presented in this work come from stimulation of the pupil using 3 pulses of light with the intention of eliminating noise by situations beyond the control of the experiment, such as blinking and / or poor measurements.

2. Theoretical Description

For the development of this work some theoretical concepts must be considered. There are the following:

2.1. Hough Circle Transform

Hough circle transform is a technique for characteristics extraction that seek to find circular shapes of certain radius r in an image. This technique is based on the fact that a circle

in an image is described by equation 1 where x and y are edge coordinates of the circular shape, a and b are the coordinates of the centroid of the shape and r is the radius of the same shape, as it is shown in [10] and [11].

$$(x-a)^2 + (y-b)^2 = r^2 \quad (1)$$

2.2. Wilcoxon Signed-Rank Test

The Wilcoxon signed-rank test is a non-parametric test that seek for differences between two groups of samples based on the magnitude of their ranges, examines the null hypothesis that both groups do not present a significant difference [12]. The test consists of:

1. Get the differences between measures, differences equal to zero are eliminated and the number of elements decreases accordingly.
2. Differences are taken as absolute values and are ranked starting from the smallest absolute difference assigned to this 1, in case of two or more differences were equal, the rankings are averaged to this absolute differences.
3. Calculate the rank sum for the negative differences T^- and for the positive differences T^+ .
4. Select from T^- and T^+ the smallest value and take it as our test statistic T to prove our null hypothesis.

The lower the value of T , the greater the value of evidence in favor of rejection of the null hypothesis [13].

2.3. Correlation Coefficient

The correlation coefficient is a measure of the independence between two variables x and y , and is given by equation 2, where \bar{x} is the mean of all the x_i and \bar{y} is the mean of all the y_i [14]. When the correlation is significant, the value of r is a way of representing its force [15].

$$r = \frac{\sum_i (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_i (x_i - \bar{x})^2} \sqrt{\sum_i (y_i - \bar{y})^2}} \quad (2)$$

2.4. Least Squares

Least squares is a technique in which given a set of parried values we seek for a mathematical function that approximate to these values. This is achieved by minimizing the sum of the squares of the differences between the input data and the data generated by the proposed function. Equation 3 show how to calculate least squares where y_i is the input value and $f(x_i)$ is the result of the evaluation of the proposed function [16].

$$S = \sum_{i=0}^n (y_i - f(x_i))^2 \quad (3)$$

2.5. Mean Squared Error

The mean square error was calculated using equation 4

where n is the total number of points, x is the original value and \bar{x} is the adjusted value.

$$MSE = \frac{1}{n} \sum_{i=0}^n (\bar{x}_i - x_i)^2 \quad (4)$$

3. Experimental Setup and Results

For this experiment we used a pupilometer designed and developed in reference [17], which serves as an artificial vision system. This instrument has two arrays of leds, one of them in the infrared spectrum and the other one in red, within the visible spectrum. It has a webcam with which, in addition to recording the experiment, allows us to locate the

instrument to have a better eye catching. All of this is controlled by a desktop application in which the lighting protocol is configured in addition to giving a real-time view of the experiment. Figure 1 shows a diagram of the artificial vision system.

For this work, six individuals participate in the experiment, 3 masculines and 3 feminine, their average age is 23.5 years. They answered a brief questionnaire, where we ask about some habits and physiological processes that we suppose could influence the individual's pupillary response as if they drink alcohol, smoke cigarettes, and if the women were in their period, these answers can help us to identify some factor that could affect the results of this experimentation, their answers are shown in table 1.

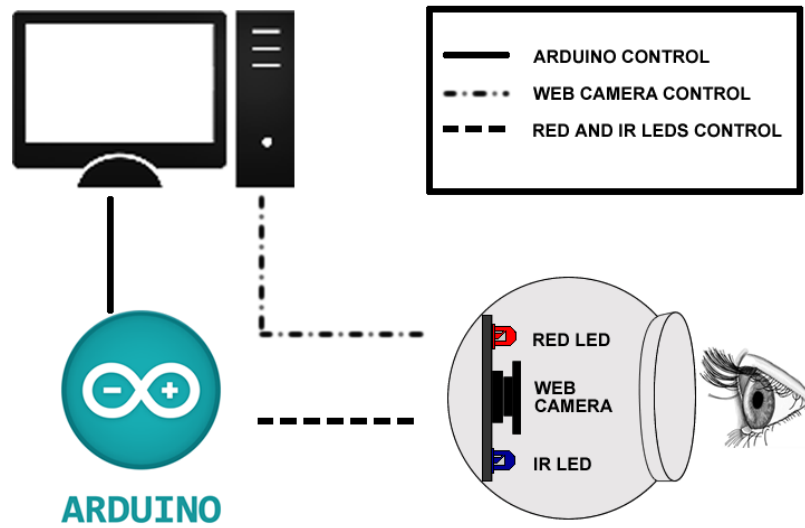


Figure 1. Artificial vision system diagram

Table 1. People Description for this Experiment

Features	People Description and Survey					
	Person 1	Person 2	Person 3	Person 4	Person 5	Person 6
Age (years old)	18	25	23	24	26	25
Gender	Female	Female	Male	Male	Male	Female
Weight (Kg)	61	48	66	115	91	90
Height (m)	1.62	1.50	1.75	1.77	1.67	1.65
Eye diseases	None	None	Astigmatism, Farsightedness	None	Myopia	None
Do you drink alcohol?	No	No	Yes	Yes	Yes	No
How much alcohol you drink a month?	N/A	N/A	16	20	10	N/A
Do you smoke cigarettes?	No	No	No	Yes	No	No
How many cigarettes you smoke per month?	N/A	N/A	N/A	5	N/A	N/A
How many hours a week you exercise?	2	1	0	0	10	0
You take care of your diet?	Yes	Yes	No	No	No	No
Last menstrual cycle?	Oct/5/2016	Oct/5/2016	N/A	N/A	N/A	Oct/7/2016
Type of menstrual cycle?	Regular	Regular	N/A	N/A	N/A	Irregular

The experiment consists of stimulating the right eye's pupil, with a protocol of illumination of three red pulses of light, each pulse has a duration of 2 seconds and a rest time between pulses of 2 seconds with infrared light illumination, we also record 2 second before the first pulse to calculate the Baseline Diameter (BD) and compare amplitudes. This lighting protocol is used following the recommendation of use long periods of illumination found in [18]. Samples taken from patients were performed under two conditions; Before their first meal and the second 30 minutes after eating food with the aim of comparing results, this samples were tagged as Sample 1 and Sample 2 respectively for everyone.

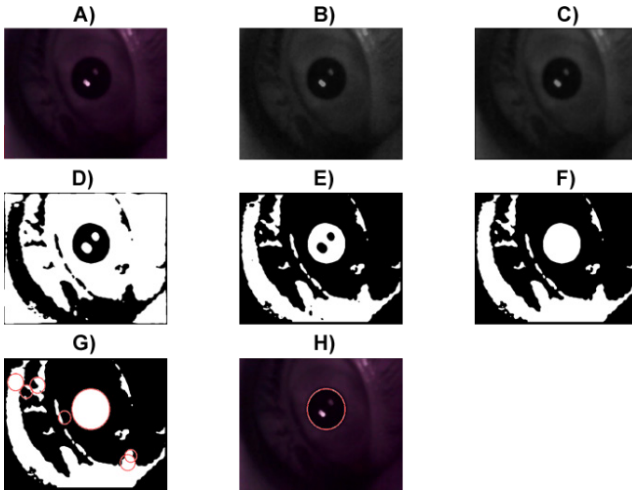


Figure 2. Graphical representation of the methodology for pupil measurement

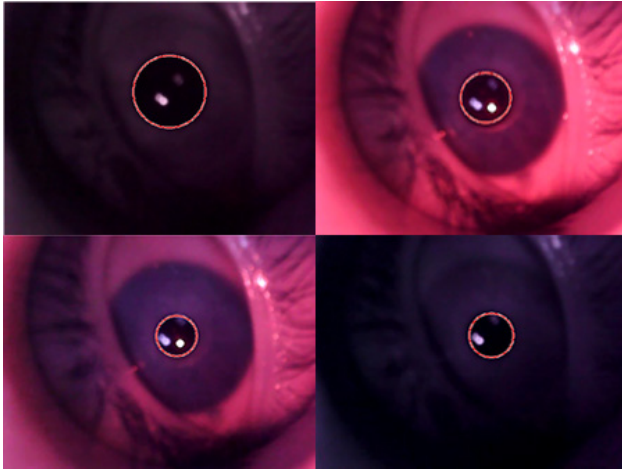


Figure 3. Results of the methodology at different light wavelengths

Once the video of each experiment is obtained, it is processed frame by frame with the objective of measuring the change of the pupil diameter respect to the time during the experiment. To achieve this, first we extract one frame from the video (figure 2 A), then we convert it to grey scale next, to enhance the contrast we apply a Gaussian filter (figure 2 B and C), then we binarize the image (figure 2 D), after that we reverse the result and finally we fill the black

holes of the resultant image (figure 2 E and F), that is to obtain a good result when we look for circular and bright shapes, then, through the circular transform of Hough, we proceed to find and identify this circular figures (figure 2 G), if there is more than one circle we select the centroid of the figure that is closest to the centre of the image in a 150 pixels area (figure 2 H).

These radii are stored in an array that at the end of the process will be saved in a text file. The results of pupil measurement are shown in Figure 3, on the other hand, in Figure 4 we can see a flow chart with the methodology used.

Once the text file with the pupil measurements is generated, features such as baseline diameter, minimum diameter, response amplitude, re-dilation amplitude, percentage of baseline diameter, response time, re-dilation time, average constriction velocity and average Re-dilation velocity, per [19]. These characteristics allow us to reduce the dimensionality of the problem, instead of comparing 104 average measurements per video, a standard of 9 characteristics is defined that completely describe the behavior of the pupil.

To obtain a logical-mathematical understanding of the signal obtained and with the idea of being able to reproduce it for future technological applications, a polynomial was approximated as a function of time by means of the method of least squares. 3 types of simulated signals that approximate the behavior of the obtained signal and that could support the interpretation of the biological signal studied and from pupillary reaction to controlled stimuli were approached. These signals correspond to a periodic signal whose function is shown in equation 5, a sigmoidal signal according to equation 6, and an aperiodic signal represented in equation 7.

$$f(x) = \sin(x) \quad (5)$$

$$f(x) = \frac{1}{1 + e^{2.8x}} \quad (6)$$

$$f(x) = -1e^{-0.3x} \cos(5x) + \sin(5x) \quad (7)$$

Different degrees of polynomial approximation were evaluated, from grade 0 to grade 100. This interval was chosen because the samples had 104 points on average. The mean square error (MSE) was taken as the selection criterion, choosing the approximation that had the lowest MSE. The results of the approximations are shown in Figures 5 to 8.

The coefficients obtained from each of the participants' samples are shown in table 2, these represent the coefficients of a polynomial of the form shown in equation 8, and in table 2 are represented as column vector in which the first row represents p_1 , the second row represent p_2 and so on. This form of representation was chosen by the length of the coefficients and the polynomials.

$$p(x) = p_1x^n + p_2x^{n-1} + \dots + p_nx + p_{n+1} \quad (8)$$

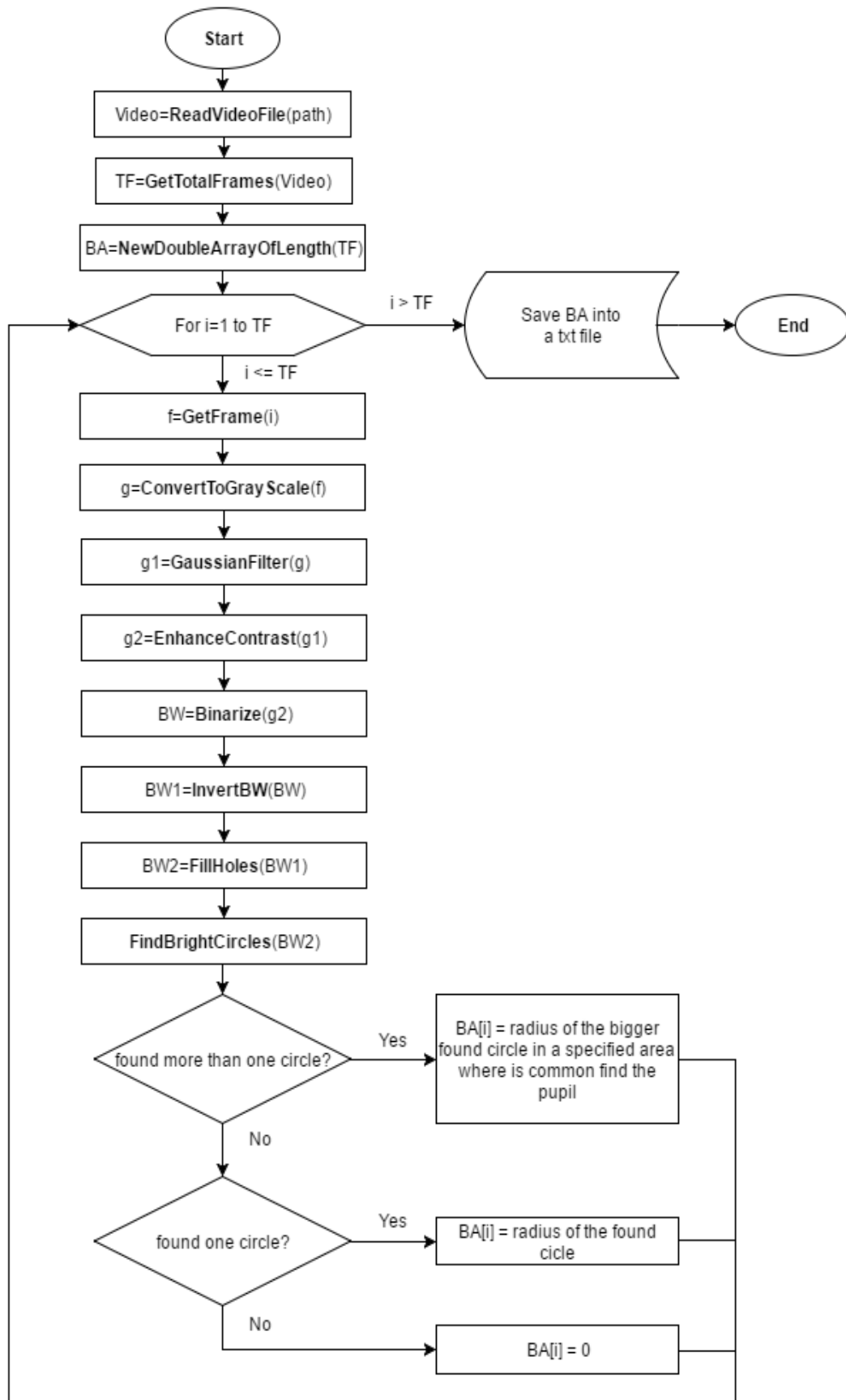


Figure 4. Flowchart of the methodology for pupil measurement

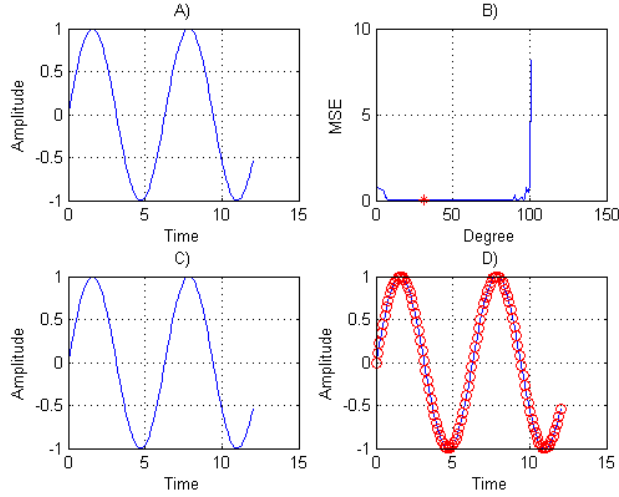


Figure 5. Periodic signal (5). A) original data. B) MSE of each tested degree. C) Adjusted data to degree 31 with less MSE. D) Show how C) fits on A)

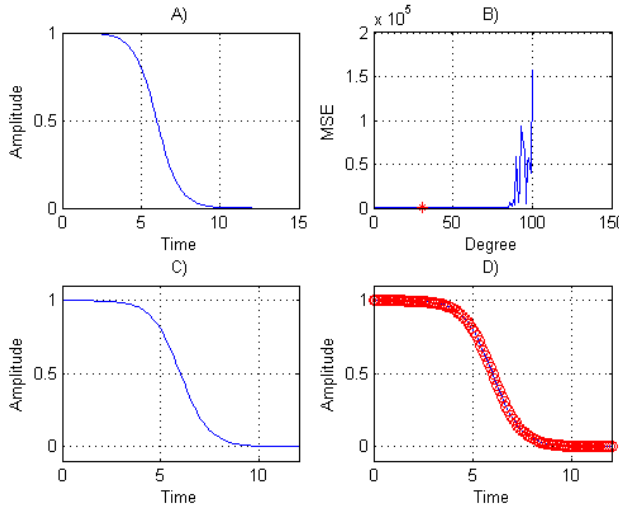


Figure 6. Nonlinear signal (6). A) original data. B) MSE of each tested degree. C) Adjusted data to degree 31 with less MSE. D) Show how C) fits on A)

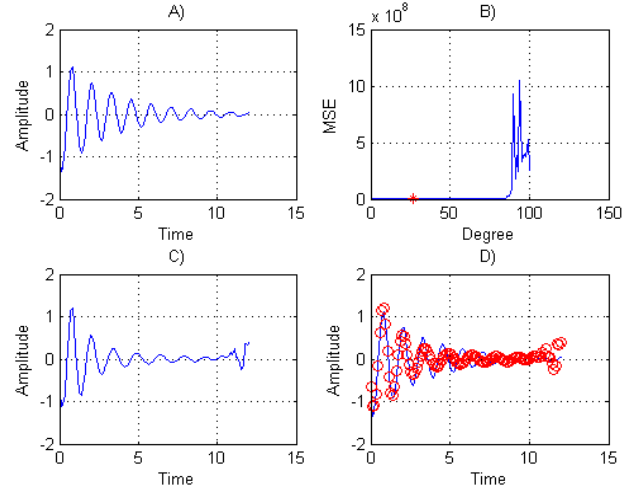


Figure 7. Aperiodic signal (7). A) original data. B) MSE of each tested degree. C) Adjusted data to degree 27 with less MSE. D) Show how C) fits on A)

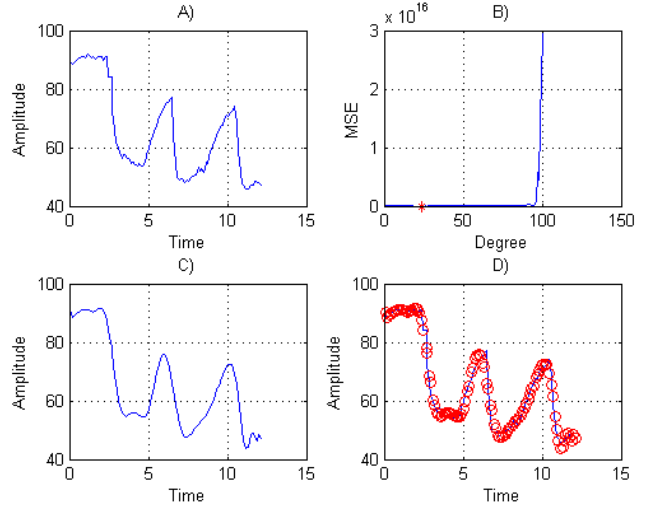


Figure 8. Biological signal from person 6 sample 2. A) original data. B) MSE of each tested degree. C) Adjusted data to degree 23 with less MSE. D) Show how C) fits on A)

Table 2. Coefficients of Samples Obtained from Least Squares (Persons 1 to 3)

	Coefficients of Samples					
	Person 1		Person 2		Person 3	
	Sample 1	Sample 2	Sample 1	Sample 2	Sample 1	Sample 2
x^{26}	0	0	0	0	0	6.0753E-15
x^{25}	0	0	0	0	0	-7.6309E-13
x^{24}	0	0	0	0	0	4.2979E-11
x^{23}	0	0	0	0	0	-1.4063E-09
x^{22}	0	0	5.9454E-12	4.3634E-12	0	2.8344E-08
x^{21}	-1.5378E-11	0	-8.3818E-10	-5.8491E-10	-2.8647E-11	-3.1436E-07
x^{20}	2.0722E-09	-9.1936E-11	5.5067E-08	3.6671E-08	3.723E-09	1.0559E-08
x^{19}	-1.2992E-07	1.0807E-08	-2.2389E-06	-1.4288E-06	-2.2469E-07	6.7219E-05
x^{18}	5.0308E-06	-5.8699E-07	6.3087E-05	3.8764E-05	8.357E-06	-0.00131435
x^{17}	-0.00013465	1.955E-05	-0.00130751	-0.00077767	-0.00021436	0.01418486
x^{16}	0.00264198	-0.00044677	0.02064365	0.01195404	0.00402048	-0.08856307
x^{15}	-0.03932908	0.00742756	-0.2537238	-0.14393823	-0.05704834	0.12628297

	Coefficients of Samples					
	Person 1		Person 2		Person 3	
	Sample 1	Sample 2	Sample 1	Sample 2	Sample 1	Sample 2
x ¹⁴	0.45349513	-0.09295028	2.45966851	1.37602604	0.62498073	3.76500879
x ¹³	-4.09989869	0.89371274	-18.9417686	-10.5205271	-5.34778298	-47.5909006
x ¹²	29.2347605	-6.68066396	116.149273	64.4836666	35.9267735	336.370302
x ¹¹	-164.587962	39.040042	-566.089705	-316.250795	-189.492505	-1669.77238
x ¹⁰	729.164719	-178.411339	2180.27689	1233.51637	780.95393	6172.63165
x ⁹	-2522.89446	634.800438	-6569.81598	-3786.64562	-2490.97955	-17290.8113
x ⁸	6735.62063	-1742.2132	15261.2401	9009.06499	6059.01223	36686.0215
x ⁷	-13638.5958	3633.9141	-26771.8938	-16260.9353	-11006.4996	-58243.7891
x ⁶	20455.3643	-5639.36207	34484.9059	21629.7055	14516.4757	67620.0798
x ⁵	-22006.5151	6326.10543	-31389.5009	-20382.0979	-13395.5748	-55380.2213
x ⁴	16249.6041	-4935.49394	19134.6824	12878.5228	8250.32939	30297.4289
x ³	-7737.65348	2532.05956	-7214.72308	-5034.08514	-3203.74674	-10173.9934
x ²	2168.24528	-774.529691	1473.83959	1067.82039	736.561439	1829.78118
x ¹	-309.70074	115.513373	-119.70861	-94.4686581	-92.5177036	-142.902056
X ⁰	107.463809	50.9250563	62.2647124	65.2964388	91.3603739	82.4172294

Table 3. Coefficients of Samples Obtained from Least Squares (Persons 4 to 6)

	Coefficients of Samples					
	Person 4		Person 5		Person 6	
	Sample 1	Sample 2	Sample 1	Sample 2	Sample 1	Sample 2
x ²⁶	0	0	0	0	0	0
x ²⁵	1.234E-14	0	0	0	0	0
x ²⁴	-1.61E-12	0	0	0	0	0
x ²³	9.603E-11	0	0	0	2.2483E-14	0
x ²²	-3.40E-09	-5.4106E-12	-8.969E-12	0	-1.6645E-11	0
x ²¹	7.895E-08	6.8588E-10	1.1598E-09	-2.9878E-11	1.9561E-09	-3.0124E-11
x ²⁰	-1.20E-06	-4.0250E-08	-6.9652E-08	3.9780E-09	-1.1375E-07	3.8656E-09
x ¹⁹	1.052E-05	1.45018E-06	2.5779E-06	-2.4645E-07	4.14811E-06	-2.3024E-07
x ¹⁸	-1.13E-06	-3.5862E-05	-6.5817E-05	9.43125E-06	-0.00010513	8.44661E-06
x ¹⁷	-0.001523	0.00064461	0.00122927	-0.00024956	0.00195529	-0.00021355
x ¹⁶	0.0263194	-0.00869721	-0.01738162	0.00484403	-0.02759167	0.00394462
x ¹⁵	-0.2711178	0.08964593	0.18996016	-0.07138444	0.30118874	-0.05506299
x ¹⁴	1.9696864	-0.71115403	-1.62414501	0.81561719	-2.57176367	0.59261801
x ¹³	-10.51386	4.33482147	10.9286308	-7.31506575	17.2603000	-4.97285990
x ¹²	41.253886	-20.0597548	-57.9382632	51.8184215	-91.0049751	32.6874637
x ¹¹	-114.8608	68.4954116	241.256186	-290.292399	374.812448	-168.183805
x ¹⁰	201.89099	-161.587191	-783.516661	1282.15217	-1192.13361	673.470614
x ⁹	-109.8059	213.704689	1962.93830	-4432.30403	2873.16490	-2076.00772
x ⁸	-492.0037	49.2520520	-3736.49670	11852.1173	-5088.08290	4843.87850
x ⁷	1633.8597	-873.895842	5296.64005	-24105.2732	6269.95084	-8351.16048
x ⁶	-2605.050	1909.94368	-5441.91027	36437.8988	-4753.48223	10287.7602
x ⁵	2532.8051	-2247.30999	3892.18508	-39681.8003	1252.41770	-8641.59290
x ⁴	-1536.632	1575.22663	-1803.93838	29838.2730	1341.52376	4626.09846
x ³	560.15568	-651.39108	461.928026	-14589.4236	-1577.20863	-1418.12514
x ²	-120.9750	151.161666	-36.6658817	4238.07021	712.619576	201.969030
x ¹	22.993335	-18.390628	-3.91631950	-627.979457	-145.797248	-7.34030030
X ⁰	73.691470	82.8051046	94.1223325	121.528762	99.5048058	67.9714453

4. Discussion

We can also conclude that the method proposed in this work will be perfectly adapted to any biological time series response with the intention of modeling it for future interpretations.

[illegible][illegible]

Table 6. Correlation Results between Extracted Characteristics and Fit Degree and Fit MSE

	Results											
	Person 1		Person 2		Person 3		Person 4		Person 5		Person 6	
	Sample 1	Sample 2	Sample 1	Sample 2	Sample 1	Sample 2	Sample 1	Sample 2	Sample 1	Sample 2	Sample 1	Sample 2
Baseline Diameter (BD)	91	53.2556	63	62	86.445	81.1877	80.048	82.5171	94.8995	87.0292	90.9467	68.07
Minimum Diameter (MD)	73	30	37	34	56.6723	56.2724	58.7504	63.5072	76.3024	59.6098	54.4579	41.8096
Response Amplitude (RA)	18	23.2556	26	28	29.7727	24.9153	21.2976	19.0099	18.597	27.4194	36.4888	26.2604
Re-Dilation Amplitude (DA)	12	25	4	11	12.1121	13.2275	14.2139	12.4606	11.9329	11.5225	17.761	17.3773
Percent of Baseline Diameter (%BD)	80.2198	56.3321	58.7302	54.8387	65.5588	69.3115	73.394	76.9625	80.4035	68.494	59.8789	61.4215
Response Time (RT)	1.0781	1.3431	1.1411	1.8521	1.5171	1.9041	1.0161	1.0291	1.3541	1.8391	1.8661	0.8991
Re-Dilation Time (DT)	3.0182	2.6812	2.8782	2.1621	2.5501	2.1161	3.0762	3.0452	2.6782	2.2711	2.1611	3.1282
Average Constriction Velocity (ACV)	16.6966	17.3152	22.7857	15.1179	19.6249	13.085	20.961	18.4731	13.7341	14.9091	19.5534	29.209
Average Re-Dilation Velocity (ADV)	3.9759	9.3243	1.3898	5.0876	4.7496	6.2508	4.6206	4.0919	4.4556	5.0735	8.2184	5.5551
Fit Degree	21	20	22	22	21	26	25	22	22	21	23	21
Fit ECM	2.1699	2.2421	2.2788	1.9106	1.9281	2.2374	1.6975	1.6196	1.4533	2.127	2.554	1.8412

Table 7. Coefficients Correlation Test Results from Table 5

	Coefficients Correlation Test RValues	
	Fit Degree	Fit ECM
BD	0.2314	-0.1710
MD	0.2023	-0.3745
RA	0.0218	0.6084
DA	-0.1749	0.1523
%BD	0.1976	-0.5260
RT	0.2327	0.4539
DT	-0.2360	-0.4621
ACV	-0.1988	0.0102
ADV	-0.0353	0.3668

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