# Title

Time distributed data analysis by Cosinor.Online application

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Cosinor.Online application

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# Abstract

Physiological processes oscillate in time. Circadian oscillations, over approximately 24-h, are very important and among the most studied. To evaluate the presence and significance of 24-h oscillations, physiological time distributed data (TDD) are often set to a cosinor model using a wide range of irregularly updated native apps. If users are familiar with MATLAB, R or other programming languages, users can adjust the parameters of the cosinor model setting based on their needs. Nowadays, many software applications are hosted on remote servers running 24/7. Server-based software applications enable quick analysis of big data sets and run on a wide range of terminal devices using standard web browsers. We created a simple web-based cosinor application, Cosinor.Online. The application code is written in PHP. TDD is handled using a MySQL database and can be copied directly from an Excel file to the webform. Analysis results contain information about setting the 24-h oscillation and a *unique ID* identifier. The identifier allows users to reopen data and results repeatedly over one month or remove their data from the MySQL database. Our web-based application can be used for a quick and simple inspection of 24-h oscillations of various biological and physiological TDD.



# Keywords

cosinor analysis, web application, PHP, MySQL, time distributed data

# 1 Introduction

In living systems, processes vary over time because of the integration of biological and environmental interactions. Among the most important and most studied are circadian processes, which are oscillations that occur approximately 24-h. During regular light/dark conditions, 24-h oscillations are very prominent in physiological systems. Physiological changes [1], responses to stress [2], behavioural activities [3] and pathophysiological events are characterised by circadian changes [4]. Removal of the main circadian pacemaker, the suprachiasmatic nucleus [5], or shifts in the regular light/dark environment [4] diminish circadian amplitude [6], which can lead to loss of stress predictability [7] in the short term manner. Over the long term, disturbing the circadian oscillations can change system-level set points and may lead to pathological processes [8–10] including cancer development [11].

The presence and significance of 24-h oscillations in measured time distributed data (TDD) can be done using cosinor analysis and the cosinor model. From a simple cosine function, we can estimate mesor, amplitude, and acrophase. In general, physiological functions can be better described by a complex series of harmonic functions [12].

The simple cosine function can be evaluated with a wide range of locally installed native applications [13,14]. Skilled users can use the MATLAB or R programming languages, which allow users to adjust the cosinor code, change the input form of the time series (radians, degrees, hours or decimal) or adjust estimated period lengths and other parts of the cosinor model [14,15].

With or without programming skills, evaluation of 24-h oscillations must be often done on the same computer. On the other hand, at present, many software applications are hosted on servers running 24/7. Besides that, server-based software applications enable quick analysis of big data sets and run on a wide range of terminal devices using a standard web browser only.

Therefore, we created a web-based cosinor application, Cosinor.Online. Application code is written in PHP (hypertext preprocessor), a server-side scripting and general-purpose programming language designed for web development. Input data are handled by MySQL and can be copied directly from an Excel file to the webform.

# 2 Mathematical modelling and code writing

We wrote our code in PHP in line with the MATLAB code [15], which implements a standard cosinor method [14,16]. In the beginning, we solved a system of linear equations (Equation 1). Because of PHP implementation, we used matrix inversion instead of Gauss-Jordan elimination. In extreme cases, if the matrix is badly conditioned, this approach can provide false results.

$$\begin{bmatrix} n & \sum x_i & \sum z_i \\ \sum x_i & \sum x_i^2 & \sum x_i z_i \\ \sum z_i & \sum x_i z_i & \sum z_i^2 \end{bmatrix} \cdot \begin{bmatrix} M \\ A\cos\varphi \\ A\sin\varphi \end{bmatrix} = \begin{bmatrix} \sum y_i \\ \sum x_i y_i \\ \sum y_i z_i \end{bmatrix} \qquad (1)$$

From the Equation 1, where $x_i = cos(\omega t_i)$, $z_i = sin(\omega t_i)$ and $n$ is a number of input values, we obtained mesor ($M$), $A\cos\varphi$ and $A\sin\varphi$ from which we calculated amplitude ($A$) (Equation 2). Using inverse tangent in radians and the signum function [15] we estimated acrophase ($\varphi$).

$$A = \sqrt{(A\cos\varphi)^2 + (-A\sin\varphi)^2} \qquad (2)$$

Mesor, amplitude and acrophase were entered into Equation 3 and we did cosine fit to original TDD.

$$f = M + A\cos(\omega t + \varphi) = M + A\cos\omega t\cos\varphi - A\sin\omega t\sin\varphi; \qquad (3)$$

The significance of model fitting was done using the *p-value* as the F probability density function [15].

Input and output cosinor data are handled and temporarily stored in the MySQL database. Using a *unique ID* string, users can delete input and output data immediately after the analysis is complete. If the user does not delete their data, all data is automatically deleted one month from the beginning of the analysis. Any other data (e.g. operating system, browser, country, etc.) are not stored in our database. Temporarily stored input and output data are not used for any other analyses. Storing data in a MySQL database is only a technical implementation to allow users to reload older analyses on different devices at various times.

From the MySQL database, data are loaded using a randomly generated *unique ID* string. Original input data are visualized as a scatter plot with a cosine fit as a line plot. Due to online usage, cross-platform and cross-browser compatibility, we used Google Charts [17], which are very easy to use for online visualization of a wide range of data.

# 3 Software usage

Software codes are hosted on the encrypted domain and the application is available at https://cosinor.online address.

## 3.1 Input data

Cosinor.Online application consists of several pages. On the input page, users can enter time and experimental values in decimal form, thus, 8:00 am is 8.00, 8:15 am is 8.25, 8:00 pm is 20.00, 8:15 pm is 20.25 and so forth (Figure 1).

Time and data columns must be the same size; if data is missing from a certain time point, the relevant time-row must be removed.

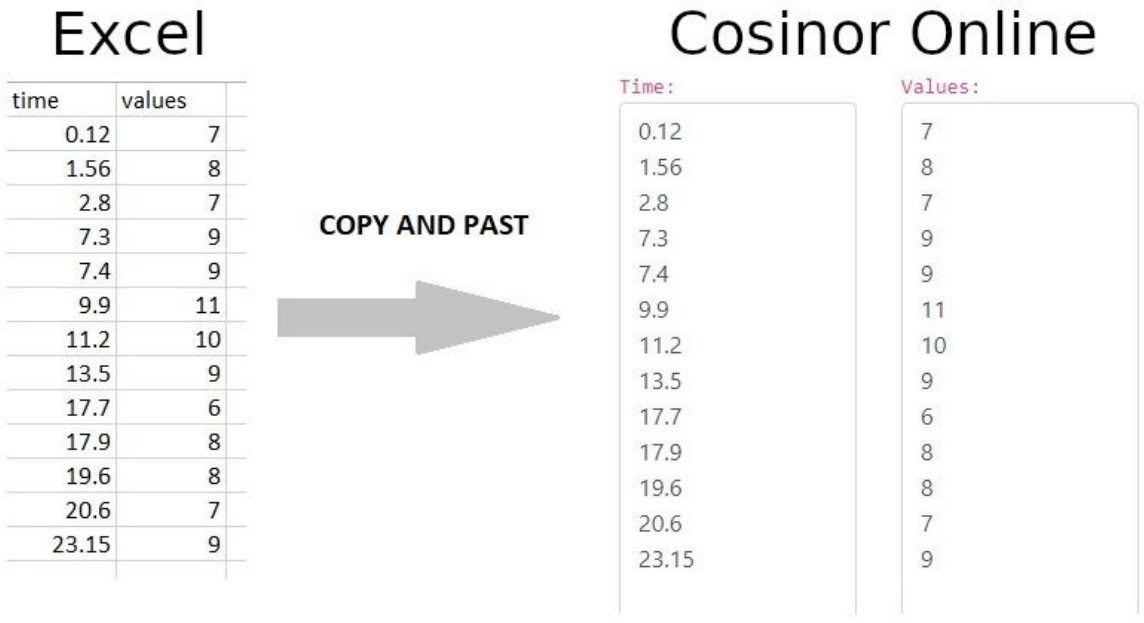


**Figure 1:** Loading data is very easy: users can simply copy and paste columns from an Excel file to the webform. Time and data columns must be the same size; if data is missing from a certain time point, the relevant time-row must be removed.

## 3.2 Output data

After the submission of the input TDD, users can see results and outputs from the model describing 24-h oscillations in the loaded data. Original and calculated data are shown in a table and visualized in the chart (Figure 2). Mesor is the average value around which the variable oscillates. Amplitude is the difference between the peak (or trough) and the mean value of a wave. Acrophase is the time of peak activity [12,13,16]. The application produces mesor and amplitude in the units of user's input data; acrophase is provided in hours, decimal form. Chart's title, as well as vertical and horizontal axes, are adjustable and charts are downloadable.

A

### Basic info

| | |
|---|---|
| Unique ID | *swcZ2TN64T* |
| Created | 2019-10-16 11:52:38 |
| Cosinor model period | 24 hours |

### Cosinor analysis

| | |
|---|---|
| Mesor | 8.43157 |
| Amplitude | 1.28091955000 |
| Acrophase (hours) | 9.75001653000 |

### Zero-amplitude test

| | |
|---|---|
| Df1 (*ndf, numerator*) | 2 |
| Df2 (*ddf, denominator*) | 10 |
| F-value | 5.70615 |
| P-value | 0.02222 |

B

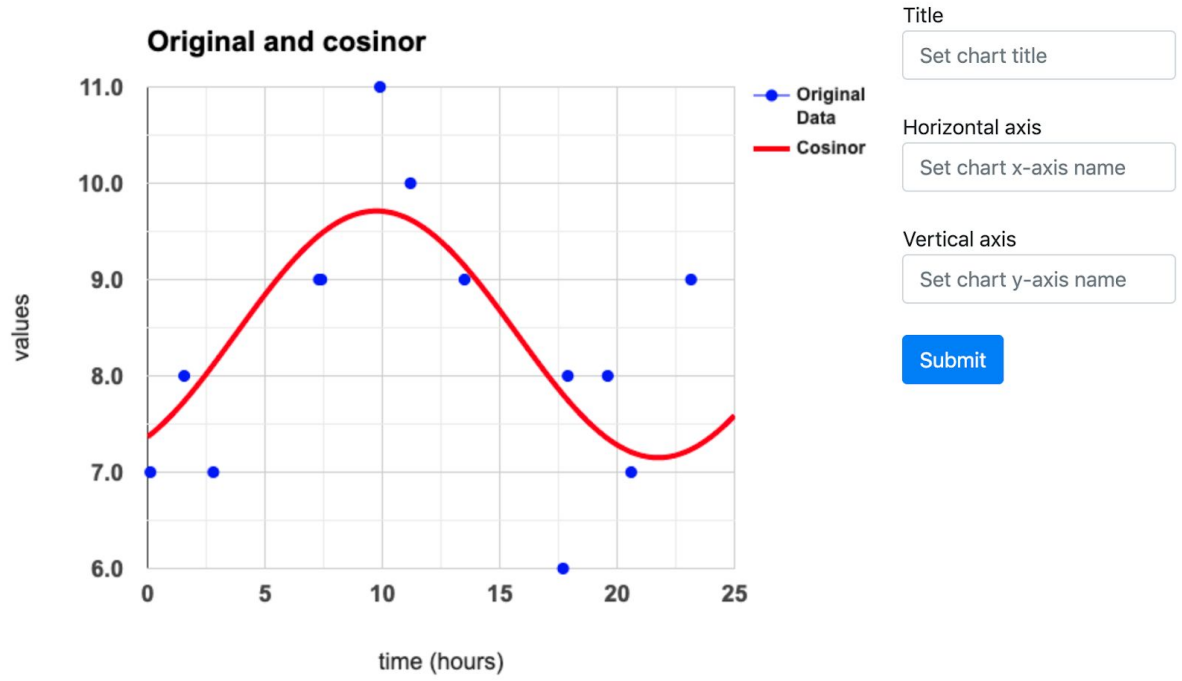


**Figure 2:** (A) On the output page users can find information about the date and time when the analysis was done as well as the *unique ID* string. Mesor and amplitude are in the units of the user's input data; acrophase is provided in hours, decimal form. (B) Original and cosinor data are plotted on the chart.

## 3.3 Reload analysis

On the output page, users can find information about the date and time when the analysis was done as well as the *unique ID* string, which can be inserted into the field on the *Reload analysis* page. Using the *unique ID* string, users can repeatedly reopen their data and results for up to one month. After this period, TDD and results are automatically removed from the database without the possibility to recover them.

## 3.4 Remove data

Using the *unique ID* string, users can remove their data immediately and permanently from the database; this function is available in the tab *Remove data*.

## 3.5 Suggestions, questions

We believe, Cosinor.Online is very intuitive web-based application intended primarily for

quick analysis of periodic data, but we are open to any suggestions for how to improve the application based on user experiences and this information can be shared in the tab *Suggestions, questions*.

# 4 Cosinor.Online versus other applications

A lot of different applications evaluate cosinor analysis, but a lot of them require installation on a local drive, a specific type/version of the operating system, and/or the presence of various add-ons. We were unable to install many of them on our hardware. Therefore we compared Cosinor.Online application to scripts/packages, which run in software environments, namely one script written for MATLAB [15] and two R packages, cosinor (written by Michael Sachs; [18]) and cosinor2 (written by Augustin Mutak; [14]).

Mesor, amplitude, acrophase and the significance of the estimated model were the same using different applications and Cosinor.Online (Table 1). Tested input data and results from a comparison of Cosinor.Online versus other applications are freely available through Google Sheets (https://bit.ly/CosinorOnlineExamples). R scripts and tested input data in text files are downloadable at https://bit.ly/CosinorOnlineRData.

**Table 1:** Outputs of cosinor analysis did not differ between Cosinor.Online, MATLAB code and R packages, cosinor and cosinor2. Details of the analyzes are available at https://bit.ly/CosinorOnlineExamples. Amp – amplitude; Acr – acrophase (peak or trough; hours, decimal form).

| | Data Set 1 | Data Set 2 | Data Set 3 | Data Set 4 | Data Set 5 | Data Set 6 | Data Set 7 | Data Set 8 |
|---|---|---|---|---|---|---|---|---|
| Mesor | 7.58 | 7.86 | 8.04 | 7.73 | 8.43 | 4.67 | 34.28 | 23.08 |
| Amp | 3.96 | 3.98 | 3.95 | 4.03 | 1.28 | n.s. | 7.92 | 6.82 |
| Acr | 11.37 or 23.37 | 11.62 or 23.61 | 11.84 or 23.84 | 12.44 or 24.44 | 9.75 or 21.75 | n.s. | 20.35 | 15.76 or 27.76 |

# 5 Discussion

Biological data vary in time and reveal significant 24-h oscillations [13]. This variability should be considered and only data from similar time points between days should be compared. Evaluation and comparison of TDD measured over the course of a day require cosinor

analysis, which can detect significant 24-h variability.

Cosinor analysis can be done with locally installed native applications or using the MATLAB [15] or R [14] programming languages. Anyway, evaluation of 24-h oscillations is often limited to the same computer. We found online available applications, but there are using outdated VBScript and ActiveX components that many modern web browsers do not support. Thus, server-side software applications, in which software is hosted on servers running 24/7, could be a solution. End users only need a personal computer, tablet or just a phone with a standard web browser, so the user's low power devices can serve as terminals to connect to a specific server with a specific request.

To take advantage of these changes, we created Cosinor.Online applications using PHP and MySQL in line with the MATLAB code [15]. Input and output data are visualised using Google Charts. Cosinor.Online application thus provides cross-platform and cross-browser compatibility as well as the availability of data 24/7.

Some advanced and sophisticated chronomics online available analysis toolkits exist. However, they do not allow to store data and are a bit complicated, mostly for beginners and students. On the other hand, Cosinor.Online application is a very simple web-based application. Loading TDD is easy: users can simply copy and paste columns from an Excel file to the webform. Input and output data are processed in the background using PHP and MySQL on the servers. Input and output data are stored on the servers. Users can adjust titles in charts and download charts.

Individual analyses are given an original, randomly generated *unique ID* string, which allows users to reopen or remove their data from the software's database. If users do not remove their data, they are stored for up to one month. However, after this period, stored data are automatically and permanently removed from the MySQL database.

Our purpose was to create a very simple and intuitive web-based application especially for students, who have limited skills with data analysis or importing TDD into different software applications but are skilled in using a wide range of modern and permanently connected devices. We believe that our web-based application will also help experienced researchers, particularly when they simply need to do a quick inspection of their data: just copy, run and check.

However, there are some limitations to our application. Its current version fits only 24-h periods. Because of PHP implementation, Cosinor.Online application can provide false results in very extreme cases. Our web-based application does not provide confidence

intervals of mesor and amplitude.

Cosinor.Online application is available 24/7 at https://cosinor.online address. The developers are open to any suggestions for how to improve the Cosinor.Online application on the basis of user feedback.

# 6 Conclusion

We created the web-based server-side application Cosinor.Online using PHP, MySQL and Google Charts. Cosinor.Online application can be used for a quick and simple inspection of the 24-h oscillations of various biological and physiological time distributed data. Users are able to reopen the analysis on a wide range of devices for free up to one month.

# 7 Competing interest

None declared.

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