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## Novel Tools and Methods

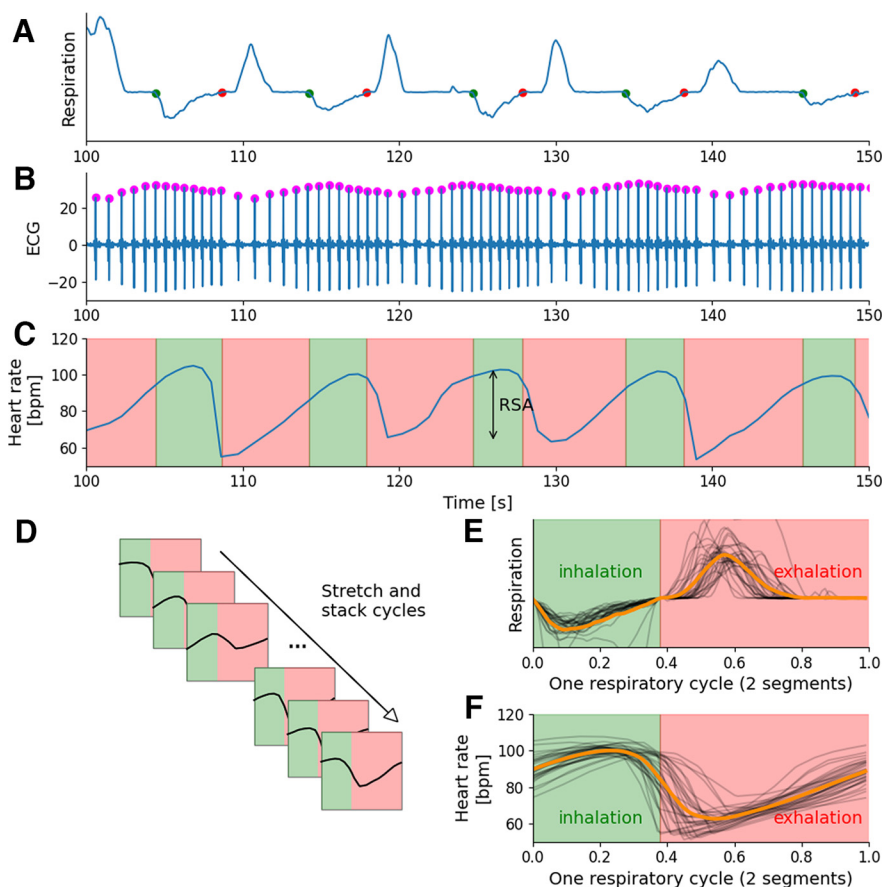
# A Unifying Method to Study Respiratory Sinus Arrhythmia Dynamics Implemented in a New Toolbox

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## Visual Abstract



Respiratory sinus arrhythmia (RSA), the natural variation in heart rate synchronized with respiration, has been extensively studied in emotional and cognitive contexts. Various time or frequency-based methods using the cardiac signal have been proposed to analyze RSA. In this study, we present a novel approach that combines respiratory phase and heart rate to enable a more detailed analysis of RSA and its dynamics throughout the respiratory cycle. To facilitate the application of this method, we have implemented it in an open-source

## Significance Statement

Respiratory sinus arrhythmia (RSA), the natural variation in heart rate synchronized with respiration, has been extensively studied in emotional and cognitive contexts. Various time or frequency-based methods using the cardiac signal have been proposed to analyze RSA. This work presents a novel approach that combines respiratory phase and heart rate to enable a more detailed analysis of RSA and its dynamics over time and throughout the respiratory cycle. It is implemented in an open-source toolbox that incorporates this framework in easily configurable functions and readable code.

Python toolbox called `physio`. This toolbox includes essential functionalities for processing electrocardiogram (ECG) and respiratory signals, while also introducing this new approach for RSA analysis. Inspired by previous research conducted by our group, this method enables a cycle-by-cycle analysis of RSA providing the possibility to correlate any respiratory feature to any RSA feature. By employing this approach, we aim to gain a more accurate understanding of the neural mechanisms associated with RSA.

**Key words:** cycle-by-cycle; respiration; respiratory sinus arrhythmia; toolbox

## Introduction

Brain and body have a strong bi-directional interaction through a wide range of rhythms, explained by the plethora of literature on the topic (Thayer and Lane, 2009; Azzalini et al., 2019; Sevoz-Couche and Laborde, 2022). Thus, noninvasive recordings of neurophysiological signals are now widely used to gain new insights in cognitive neuroscience. Many toolboxes have been developed to standardize the processing of signals, such as respiration and heart signals [electrocardiogram (ECG)], to extract respiration features, heart rate variability (HRV), and the amplitude of respiratory sinus arrhythmia (RSA; Noto et al., 2018; Makowski et al., 2021; Kirk et al., 2022).

RSA, which refers to the natural variation in heart rate synchronized with respiration, has gained significant attention as a noninvasive marker of autonomic nervous system activity and cardiovascular health (Porges, 2011). Various methods have been developed to characterize RSA, but most of them focused only on its amplitude (Grossman et al., 1990; Lewis et al., 2012).

Our group previously developed and used a framework to analyze neural events and its relations to the respiratory cycle (Roux et al., 2006). The main idea was to get a phase representation of the respiratory cycle as a normalized time basis, enabling standardized data collection across

different subjects and facilitating the averaging of respiratory driven activity. We found particularly relevant to reuse this method to analyze RSA and its dynamic along the respiratory signal. Indeed, given the link between respiration and heart rate, it appears essential to be able to characterize both (1) the RSA dynamics (2) the respiration RSA phase-locking as a function of respiration duration and/or amplitude. For this purpose, cycle-by-cycle analysis is relevant. This has already been partly tackled by previous work (Kotani et al., 2000; Gilad et al., 2005). But, to go further, combining these approaches would be particularly useful.

For this purpose, we propose a new python toolbox, named `physio`, that incorporates this framework into the classical RSA extraction pipeline, aiming at enhancing the understanding of heart rate dynamics in relation to the respiratory cycle. Our toolbox provides easily configurable functions and readable code. It includes functions for processing ECG and respiratory signals providing cycle-by-cycle respiratory features. These are necessary for computing RSA. Last but not least, users have access to key parameters concerning the normal range of heart or respiratory rate, making the toolbox applicable to both humans and animals.

## Materials and Methods

### Toolbox description

#### Overview

`physio` was developed in Python and its well established scientific toolstack (NumPy, SciPy, pandas). Code, documentation, and tutorials are freely available here:

- Code: <https://pypi.org/project/physio>
- Documentation: <https://physio.readthedocs.io>
- Notebooks for generating figures: [https://github.com/samuelgarcia/physio\\_benchmark](https://github.com/samuelgarcia/physio_benchmark)

Our method requires the processing of both ECG and respiration signals to compute RSA dynamics. Our aim was to provide for the user a possibility to access to key parameters of these two processing steps through low-

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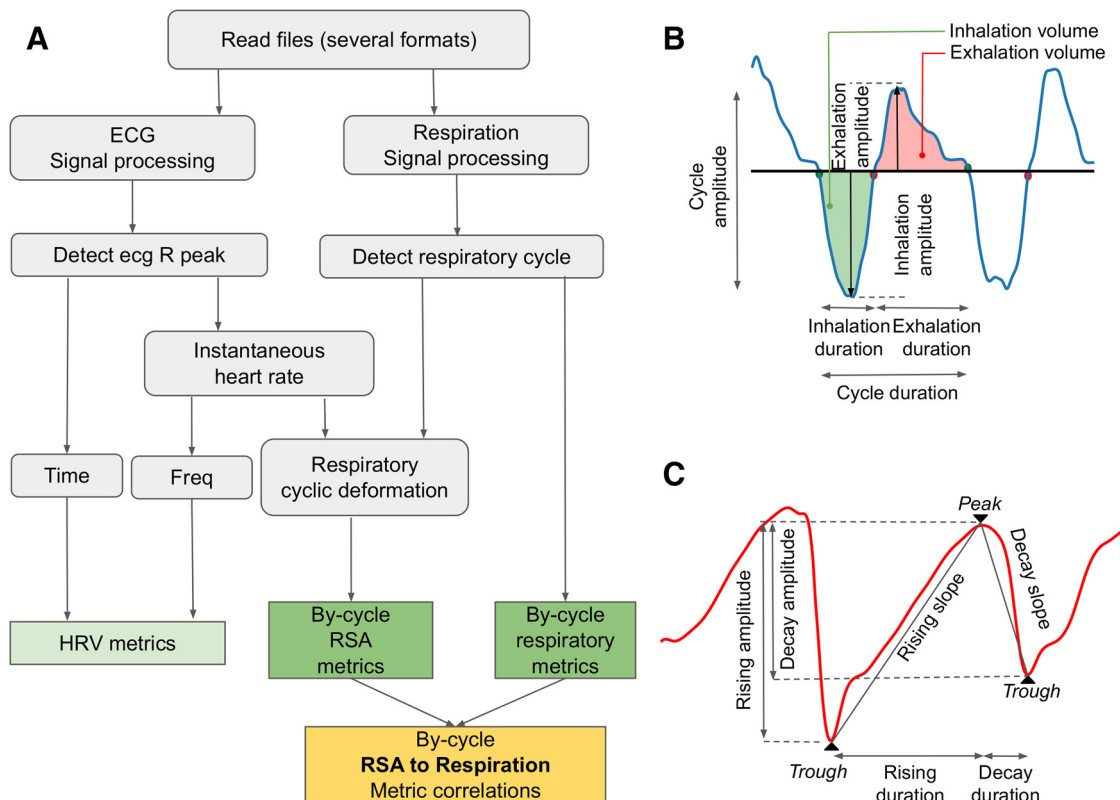
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**Figure 1.** Pipeline and features extraction. **A**, Overview of the pipeline. The dark green and yellow boxes highlight the uniqueness of the toolbox. **B**, Respiratory features. All features are individually collected for each cycle. **C**, RSA features detection. All features are individually collected for each cycle.

level functions and light readable code. Processing steps are similar for humans and animals even if key parameters could differ. In the following paragraphs, we will detail the processing steps using human model parameters (toolbox defaults). These steps are presented in a schematic view presented in Figure 1A. The different processing stages are as follows.

*Respiration cycle detection (Fig. 2A)*

The first step aims at extracting respiratory timestamps that will be used as a template to explore heart rate dynamics. Example of detection is presented in Figure 2A with inhalation starting times shown by green dots and exhalation starting times shown by red dots.

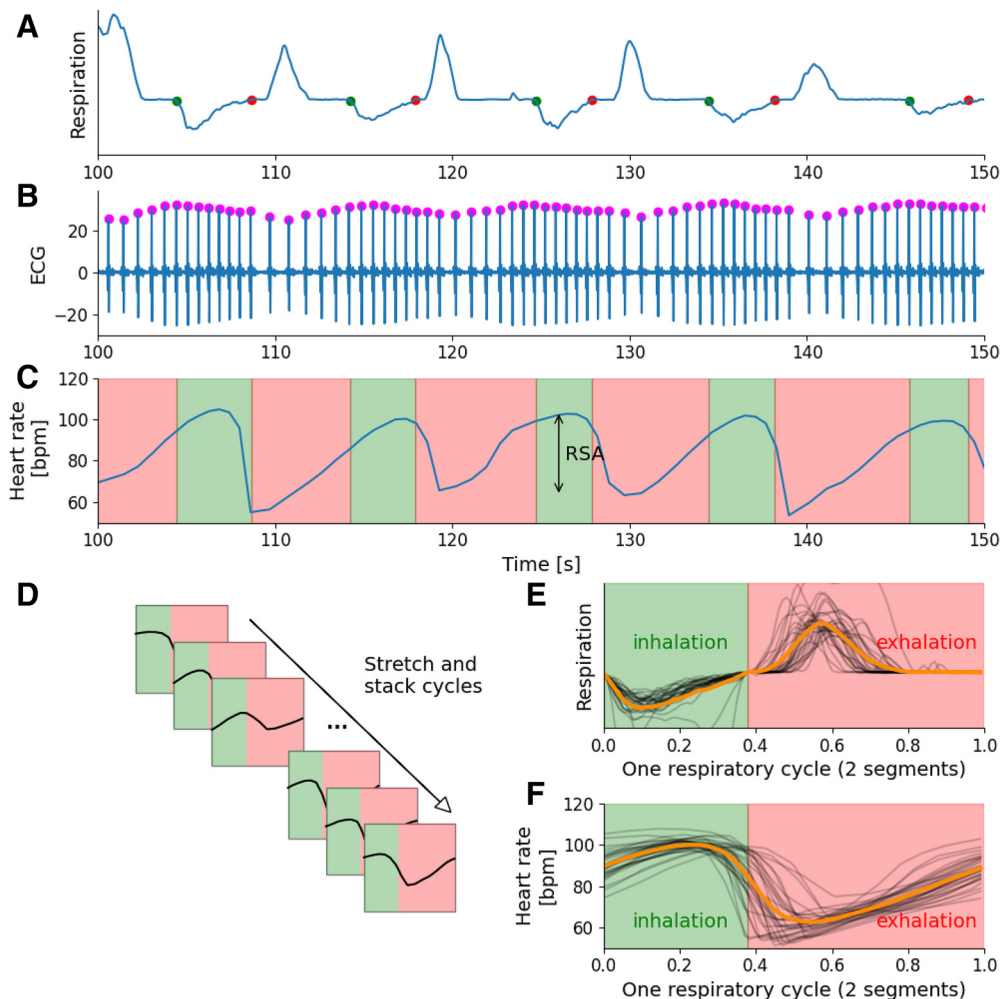
- Respiratory signal preprocessing: constant detrending (mean/median subtraction), filtering (low-pass, Bessel, 7 Hz) and optional temporal smoothing (Gaussian kernel, 60 ms, working also as a low-pass filter).
- Baseline estimation using signal median or signal mode.
- Respiratory cycle detection: baseline crossings were time-stamped, and labeled as inhalation start if corresponding signal is decaying, or labeled as exhalation start if corresponding signal is rising.
- Computing respiration features: cycle-by-cycle respiratory features such as duration, amplitude, volume (Fig. 1B).

- Cleaning respiration features: remove cycle outliers due to artifacts or poor detection, using log-transform of the respiratory volume and threshold based on the median absolute deviation (MAD; 4 by default). Thus, respiratory cycles that are too short in time and/or in amplitude are removed.

*ECG to heart rate*

The second step, consisting in processing ECG to extract heart rate dynamics across time (heart rate signal), was processing as follows:

- ECG signal preprocessing: filtering (bandpass, Bessel, 5 to 45 Hz). These parameters allow for an increase in signal-to-noise ratio, signal being the R peak, noise being outer frequency components (slow drift, P and T cardiac cycle wave, line-noise).
- Normalization: median subtraction before division by median absolute deviation (MAD) which is defined by  $k * median(|x_i - median(x)|)$  where  $k = 1.4827$  and  $x$  corresponds to the traces values. MAD provides a dispersion statistical metric that is more robust to outliers than SDs.
- R peak detection (Fig. 2B, purple dots): only the traces whose amplitude is greater than an automatically calculated threshold are kept (K MAD deviations from the median). In these traces, the peaks are detected using a sliding window which finds the local maxima.



**Figure 2.** Computational procedure for RSA extraction. **A**, Respiratory cycle detection. Baseline crossing points are detected on preprocessed signal: inhalation and exhalation starts and represented by green and red dots, respectively. **B**, R peak detection on ECG. After ECG filtering, R peaks are detected by finding local maxima (purple dot). **C**, Instantaneous Heart rate signal reconstruction. RR intervals in seconds are converted to beats per minute. RR intervals are interpolated on regularly sampled time series. Respiratory epochs are displayed by pink and green time zones for exhalation and inhalation respectively. **D**, Cyclical deformation of heart rate epochs. Heart rate signals are windowed according to respiratory cycle epochs. Each epoch time axis is rescaled to a respiratory phase basis with alternating inhalation and exhalation phases. **E**, Respiratory cycles stretched. 0: inhalation starting phase point; 0.4: inhalation-exhalation transition phase point; 1: exhalation stop phase point. The average waveform is plotted in orange. **F**, RSA dynamics along respiratory phase. With the same process, heart rate dynamics are computed and plotted along respiratory phase. Various heart rate epochs (black traces) are averaged across cycles to get the mean RSA dynamic along the respiratory phase (orange).

- R peak cleaning: only peaks separated by a minimum interval (400 ms by default) are kept for analysis.
- R-R intervals were computed by taking the time difference between R peak times. By default, RRI interval units (or heart periods) are converted to beats per minute ( $60/\text{RRI}$  time differences in seconds), units more commonly used in physiology. Note that at this step, RR time periods can be statistically characterized as a distribution whose position and dispersion metrics give access to time domain heart rate variability (HRV) metrics (mean, median, MAD, RMSSD, SD, coefficient of variation).
- Instantaneous heart rate signal construction by interpolation of RRI values on regularly sampled time vector

(default 100 Hz). This provides an instantaneous heart rate signal (in beats per minute) or an instantaneous heart period signal (in milliseconds) depending on the preferred unit. Here, frequency components of this signal can be computed through fast Fourier transform (FFT) in order to compute classical frequency domain HRV metrics (low-frequency power, high-frequency power).

#### *Respiratory phasing of RSA: method incorporation*

In the next section we provide a brief overview of the RSA extraction pipeline implementing the new framework that is more deeply explained below, Respiratory phasing of RSA.

- Cyclical deformation of heart rate signal based on respiratory cycle timestamps.
- This heart rate signal cyclically deformed is sliced according to respiratory timestamps (Fig. 2D) in order to get one trace by respiratory cycle (Fig. 2F).
- Cycle-by-cycle feature extraction of heart rate respiratory epochs. Peak to trough amplitude differences of each heart rate epoch are computed to obtain cycle-by-cycle RSA amplitude (Fig. 1C). Each heart rate deformed epoch provides one amplitude value by respiratory phase bins (default is  $N = 50$  bins). This phase-amplitude representation allows for computing features of RSA dynamics (Fig. 1C) such as rising/decaying duration, amplitude, and slope.

### Key parameters availability

The previous section outlined the primary computational steps involved in the transformation of raw signals for RSA exploration. Each major step consists of multiple substeps, and it was our intention to provide users with access to key parameters at both levels of the algorithm hierarchy. As a result, the major steps can be easily configured using a few high-level functions, using preset parameters that are appropriately adjusted for “normal” breathing humans by default, or for “normal” breathing animals such as rodents.

Depending on the experimental conditions, the respiratory features of the subjects may vary from normal to slower (e.g., slow-paced breathing) or faster (e.g., running human and/or naturally fast-breathing animals). In such cases, the traditionally set parameters of many toolboxes cannot be used, as they assume a typical respiratory frequency ranging from 0.12 to 0.40 Hz. To address this, we have made the parameters of the low-level functions accessible, allowing users to customize their analysis based on their specific experimental conditions.

### Respiratory phasing of RSA

This method is an update from several previous works (Kotani et al., 2000; Gilad et al., 2005; Roux et al., 2006). This work was initially made to deal with the rhythmic variability of respiratory cycle duration, making it impossible to average oscillatory neural patterns along respiration phase. Briefly, the time component of respiratory epochs, which can differ from trial to trial, was converted into a phase component defined as  $[-\pi, 0]$  and  $[0, \pi]$  for inspiration and expiration, respectively. As opposed to time representation, the phase representation is common to all epochs regarding the phase axis. Thus, this phase representation of the respiratory cycle can be used as a normalized time basis allowing to collect results in a standardized data format across different subjects and providing a way to average oscillatory components of the activity. This is a particularly relevant method to characterize activity such as heart rate dynamics normalized on a respiratory time basis.

The original method have been upgraded with two concepts: first, the respiratory phase is scaled into  $[0-1]$  (rather than the previous  $[-\pi, \pi]$ ) so that it can be divided

into one or more segments. For instance, the inhalation phase can be stretched to  $[0-0.4]$  and the exhalation phase  $[0.4-1]$ , this ratio can be change to fit the per subject real inhalation/exhalation duration ratio. We can also divide the respiratory cycle into more segments using extremum of inhalation or exhalation and even pauses in the respiratory phase. Example in Figure 2 are shown with two segments (inhalation/exhalation). Second, the method uses a simpler and faster linear interpolation rather than the FFT for interpolation.

This is why we reused this process as summarized in Figure 2:

- Heart rate signal is segmented into successive respiratory cycles with alternating inspiration and expiration windows.
- Each window is re-sampled with a linear interpolation that keeps the same number of bins per segment. This width is a configurable parameter that depends on the desired precision (default is  $N = 40$  bins).
- The phases of the inspiration and expiration windows are taken linearly between  $[0, 0.4]$  and  $[0.4, 1]$ . This latter parameter is configurable by the user.

Thus, instantaneous heart rate time series is re-scaled to a respiratory phase basis with alternating inhalation and exhalation phases, allowing an acute dynamic description of heart rate according to respiratory phase. See documentation of the toolbox for examples.

### Datasets

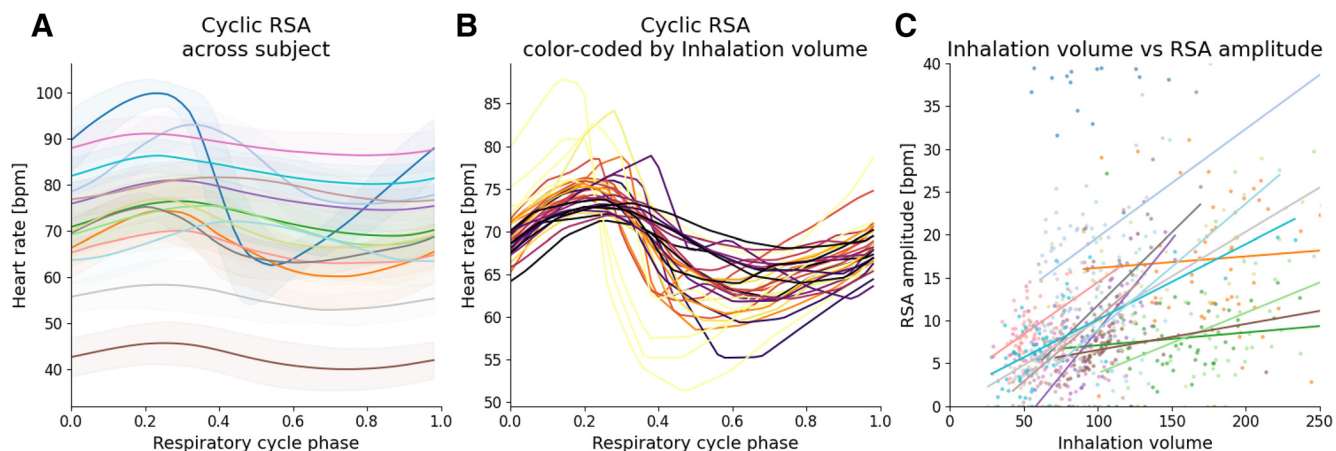
We tested our tools on two datasets coming from two free-breathing models: human and rodents (rat). Datasets are available on the Zenodo platform at <https://zenodo.org/record/8019849>.

*Human dataset.* Human dataset consisting of 15 healthy adults subjects (age:  $30.9 \pm 9.5$  years old). All participants gave informed consent to take part to the study, and all experiments were approved by the national French committee (CPP number 4090). They were sitting quietly and instructed just to relax. Recording lasted 5 min.

- Respiration signal was recorded from a nasal sensor (Sensortech GmbH) at a sampling rate of 1000 Hz, amplified by actiCHamp Plus amplifier (Brain Products GmbH).
- ECG signal was recorded from three skin electrodes (right forearm, left forearm, left iliac region), at a sampling rate of 1000 Hz (same amplifier).

### Animal dataset

Animal dataset consisting of eight healthy adults rodents (rats). The experiments were carried according to the ethical guidelines of the European Communities Council Directive of November 24, 1986 (86/609/EEC), as well as the approval 16979 of the Lyon 1 University CEEA-55 ethical committee and of the Ministry of Higher Education, Research and Innovation. Recording lasted 5 min during which they were freely behaving. Respiration signal and ECG were recorded from a thoraco-abdominal telemetric jacket (DECRO, by



**Figure 3.** Some examples of respiratory phased RSA use. **A**, Intersubject variability of the mean RSA. Subjects are color coded. Shades correspond to 1 SD. **B**, Intrasubject variability of the RSA. Cycle-by-cycle RSA of one subject are represented. Color palette, from dark to light warm colors, encodes the amplitude of the corresponding inhalation (from dark to yellow). The subject corresponds to the one colored in dark gray in Figure 1A. **C**, RSA to inhalation volume correlations. Only significant slopes are represented.

Etisense). Recordings were performed at a sampling rate of 500 Hz, amplified by Etisense acquisition unit (Etisense).

## Results

We tested our tools on both human and animal datasets. Figures 3 and 4 presents some examples of computations that can be obtained thanks to the toolbox. More examples are presented in attached Jupyter notebooks.

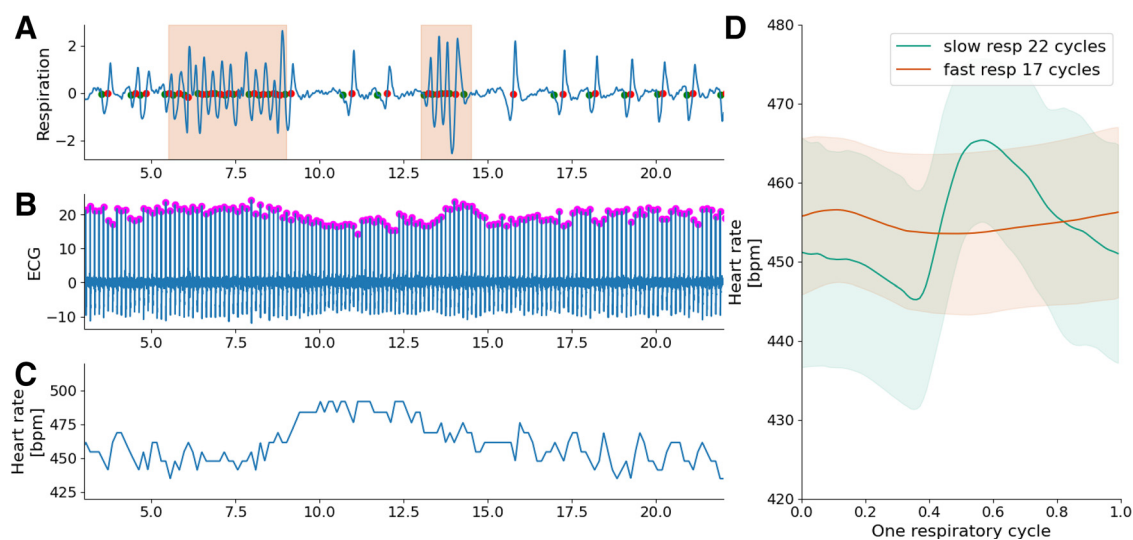
### Humans

The following outputs were obtained using the default parameters.

Cyclically deformed and sliced heart rate signal process provides a 2D array containing stacked magnitude heart rate according to respiratory phase \* respiratory cycle data

from which are computed RSA features. This can be used to get cycle-by-cycle dynamics and also the averaged heart rate dynamic across several respiratory cycle (Fig. 2F, orange trace) and the process can be iterated over subjects to display average dynamics by subject (Fig. 3A). On this latter figure, note the variability in amplitude and phase of the modulation of heart rate according to the subjects (color coded). Figure 3B allows to visualize the intrasubject variability of RSA dynamic in term of its phasing and its amplitude.

Then, two major cycle tables (also known as dataframes) can be obtained: one for cycle-to-cycle respiration features and the other for cycle-to-cycle RSA features. Both sharing the same number of rows (respiratory cycles), they can be concatenated to correlate cycle by cycle respiration to



**Figure 4.** Examples of processing rat dataset. **A**, Respiratory signal. Fast breathing periods are displayed by a shadow color zone. **B**, ECG signal. ECG peaks have been detected thanks to rodent preset of parameters. **C**, Heart rate. **D**, Respiratory phased RSA average. Average of all RSA cycles while splitting the respiratory cycle in “fast” (<600 ms) and “slow” (>600 ms). Shadow represents 1 SD on each side.

RSA features. Then, it is possible to correlate RSA features to respiration features to explore effects of respiration cycle duration-derived features or respiration cycle amplitude-derived features. Correlations could be then computed to explore, for instance, intersubject variability as shown in [Figure 3C](#) where we can see different regression slopes between subjects when exploring the RSA amplitude according to the inhalation volume.

### Animals

Switching from human to animal default preset parameters provides the same outputs. [Figure 4](#) presents an example of processing of rat data. We can see in [Figure 4A](#) some examples of detection of different types of respiratory cycles (slow or fast cycles). [Figure 4C](#) displays the instantaneous heart rate computed thanks to the previous detection of ECG peaks shown in [Figure 4B](#). Note the RSA frequency component in the heart rate that is well correlated to the respiratory signal. Cycle-to-cycle analysis allows separating RSA dynamics according to breathing cycle duration: slow respiratory cycles being correlated to larger amplitude modulation of RSA compared with fast respiratory cycles, as shown in [Figure 4D](#).

## Discussion

The `physio` package provides a new open-source python toolbox aggregating tools for processing ECG and respiratory signals to accurately characterize the respiratory sinus arrhythmia phenomenon.

RSA, the natural variation in heart rate synchronized with respiration, is one form of cardio-respiratory coupling, physiologically independent of another phenomenon, the cardio-respiratory synchronization ([Bartsch et al., 2012](#)). RSA has been the subject of numerous studies investigating the role of vagal tone under various emotional or cognitive experimental conditions. However, the computation of RSA amplitude, which serves as a potential indicator of vagal tone ([Song and Lehrer, 2003](#); [Porges, 2011](#)), has been a matter of debate throughout history ([Grossman et al., 1990](#); [Lewis et al., 2012](#)). Despite methodological variations, the literature has concluded that the different methods are equivalent ([Grossman et al., 1990](#)), leaving it to the users to choose the method that best suits their research needs. Additionally, certain studies have highlighted the varying phase patterns of the RSA phenomenon during different breathing regimes ([Kotani et al., 2000](#); [Gilad et al., 2005](#)). This is corroborated with a more recent work that evidenced the difference of vagal tone during inhalation compared with exhalation phase ([Marmorstein et al., 2021](#)). Therefore, the `physio` toolbox aims at providing a set of easily readable and configurable functions to explore both RSA amplitude and dynamics, applicable to various breathing regimes and models (e.g., normal breathing humans, slow-paced breathing humans, fast-paced breathing humans, rodents, etc.).

The main computational steps involve: (1) computing the ECG to extract the instantaneous heart rate time series (HRV metrics can also be obtained); (2) processing the respiratory signal to detect respiratory cycles and

extract respiratory features; and (3) cyclical deformation of heart rate time series on the basis of respiratory cycle time to extract cycle-by-cycle RSA amplitude modulation features in parallel with RSA dynamic features, a process adapted from a previously published method ([Roux et al., 2006](#)). These major steps are implemented through high-level functions that can be configured by the user using preset parameters. The default configuration is set for processing normal human data, but it can be adjusted for animal data as well. Customization of key computational parameters is possible through the use of easily configurable low-level functions, providing flexibility to accommodate specific experimental tasks or models that involve nonstandard physiological variables.

While there are other well-established software tools like Neurokit2, BioSPPy, that propose methods for analyzing heart and respiratory signals together, `physio` introduces some novel elements. It offers a cycle-by-cycle RSA exploration with innovative metrics, in addition to the possibility of correlating any dynamic phenomena to respiratory phase. Going back to the [Figure 1A](#), the dark green and yellow boxes highlight the uniqueness of the toolbox.

Thus, we provided human and rodent datasets from which figures and documentation have been supplied. In addition to the precise visualization of RSA dynamics along respiration phase across different subjects ([Fig. 3A](#)), we illustrated the possibility to correlate RSA features to respiratory features, enabled by the cycle-by-cycle analysis provided in the final cycle tables ([Fig. 3B](#)). As the examples displayed in [Figure 3C](#) illustrate, we can see the different regression slope when plotting RSA amplitude according to inhalation volume. One could speculate that this result is because of differences in autonomic tone between the subjects as this could modulate the relationship between respiratory cycle and RSA amplitude. Furthermore, examples of RSA dynamics along respiration phase shown in [Figure 3A](#) emphasize the intersubject variability concerning the amplitude and the phase of dynamical changes of heart rate. This visualization also highlights the pronounced steepness of the decaying phase of heart rate compared with its rising phase, around the inhalation to exhalation phase transition (see also [Fig. 2C](#)). Deep exploration of RSA dynamics is essential for uncovering the underlying neural mechanisms responsible for this phenomenon.

Thus, we firmly believe that to accomplish the objective of capturing the maximum amount of information that RSA could bring to cognitive neurosciences, it is essential to accurately extract both respiratory and ECG features for analyzing RSA amplitude in relation to the respiratory phase. Only a detailed cycle-by-cycle analysis of RSA dynamics offered by the `physio` toolbox can provide the relevant framework necessary for understanding the whole phenomenon of cardio-respiratory coupling.

In conclusion, `physio` offers valuable tools for comprehending heart rate dynamics in relation to the respiratory cycle in diverse models. It aims to achieve this by providing easily configurable functions encoded in a concise and readable algorithm, enabling researchers to adapt their analysis strategies to their specific data conditions.



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