

ValsalvaAnalyzer

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The ValsalvaAnalyzer software calculates adrenergic and vagal indices characterizing the response to the Valsalva maneuver (VM) from continuous ECG and BP measurements. To demonstrate the software, we provide a brief description of the experimental setup followed by a detailed description of the software. The software reads data extracted in MATLAB from patient records stored in LabChart. The analysis is demonstrated on a healthy control patient, but the software includes example data from eight subjects with a range of autonomic responses. Below, we discuss patient examples and describe the protocol to install and run the software. The protocol includes references to figures generated within MATLAB. To distinguish these from figures included in the representative results, these are all referred to as MFigure #.

Example patients

The software includes data (extracted as MATLAB files from LabChart) from measurements of ECG (channel 1), HR derived from ECG (channel 2), and BP (channel 3). Table 1 includes a detailed patient description and patient status notes.

Experimental setup

Example data measured during the Valsalva maneuver are collected from eight subjects with and without autonomic dysfunction (characteristics listed in Table 1). Continuous measurements of BP are obtained from a finger blood pressure cuff on the index and middle fingers on the non-dominant hand (**Fig. 1(b)**). The hand is positioned at the level of the heart to eliminate the effects of gravity (**Fig. 1(c)**). ECG is measured using a standard 3-electrode ECG. The leads are placed at equidistance from the heart at the left and right atrium and on the left side lower edge of the rib cage. The signals are saved in LabChart with channel 1 displaying the ECG, channel 2, HR extracted from the ECG, and channel 3 continuous BP (see **Fig. 1(e)**). As shown in **Fig. 1(a)**, the Valsalva maneuver is performed by exhaling into a positive end-expiratory pressure (PEP) device connected to a manometer (**Fig. 1(d)**). The subject breathes normally for 1-5 minutes until stable, steady signals are recorded. The subject is asked to exhale for 15 seconds, holding a pressure of 40 mmHg (**Fig. 1(a)**). After the VM, the subjects continue breathing normally for 1-5 minutes.

Table 1: Patient characteristics

Patient	Age (years)	Sex (m/f)	Height (cm)	Weight (kg)	BMI (kg/m ²)	Notes
Subject 1	35	m	176	92	29.7 (ob)	Normal response
Subject 2	31	m	180	70	21.6 (nw)	Normal response
Subject 3	30	m	187	93	26.6 (ow)	Large overshoot in phase IV. HR artefacts due to ECG signal noise
Subject 4	42	m	175	76	24.5 (nw)	V-response typical for autonomic dysfunction. Inadequate chronotropic effect in phase II. No BP recovery in late phase II. Missing overshoot in phase IV. Long PRT
Subject 5	37	f	165	85	31.2 (ob)	No overshoot in phase IV
Subject 6	61	f	170	107	37.0 (ob)	Inadequate BP recovery in late phase II. Maximal BP does not equal end BP in late phase II
Subject 7	42	m	177	84	26.8 (ow)	Missing overshoot in phase IV
Subject 8	58	f	166	77	27.9 (ow)	Negligible BP drop in early phase II. HR artefacts due to ECG signal noise. BP artefacts in phase IV

nw: normal weight BMI (18.5-25), ow: over-weight (BMI (25-30), ob: obese (BMI > 30)²⁶

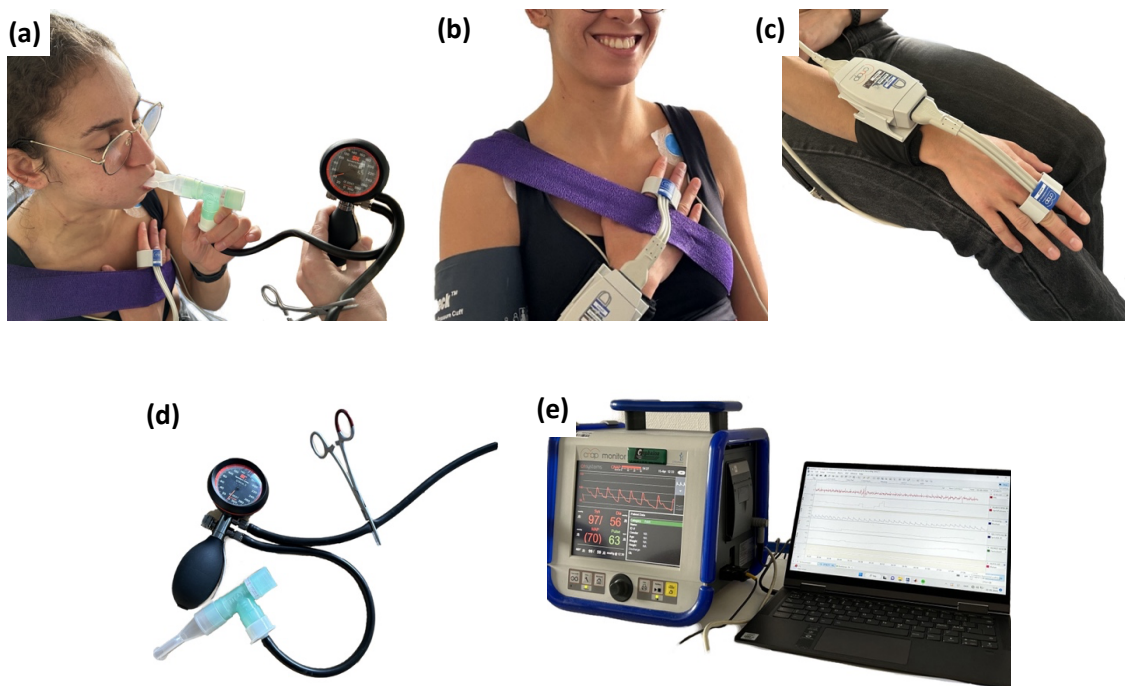


Fig. 1: (a) Subject is exhaling into a positive end-expiratory pressure (PEP) device connected to a manometer, holding an intrathoracic pressure of 40 mmHg in 15 seconds. (b) Finger BP cuffs are fastened at the level of the heart, using a cohesive bandage. (c) BP cuff mounted on index and middle fingers on non-dominant hand. (d) PEP-device attached to a manometer. (e) CNAP module continuously measures signals and is connected to a computer that processes and saves data using LabChart.

Software

Step 1: Software installation, data upload, and startup

VM data should be exported in MATLAB format. This protocol describes how to interface data recorded in LabChart with MATLAB. However, the protocol does not depend on recordings stored in LabChart; it requires that signals be stored in specific channels. We refer to their manuals for signals recorded by other software and note that conversion may be needed to export recordings in the correct format. Data should include continuous time-series measurements of ECG and BP.

- 1.1. Download the ValsalvaAnalyzer Software (MATLAB and LabChart).
- 1.2. Clone the GitHub Repository at <https://github.com/msolufse/ValsalvaAnalyzer>.
 - 1.2.1 Click the green *code* button. Click download zip.
 - 1.2.2 Navigate to the files located in the folder “ValsalvaAnalyzer”. The software consists of MATLAB scripts. The main script DriverBasic.m is in the main folder “ValsalvaAnalyzer” and all other scripts (.m files) are in the folder “Core”. The ValsalvaAnalyzer also includes folders “Figures”, “Markers”, “Optimized”, “Sensitivities”, and “WS”. “Figures” stores generated figures. The folder includes two subfolders, one for figures generated from the data “Data” and one for figures generated by the differential equations model “Model_fits”.
 - “Labchart” include “.mat” files exported from LabChart.
 - “Markers” holds Excel sheets with clinical ratios (one file per subject).
 - “Sensitivities” and “Optimized” include .mat files with sensitivities and estimated parameter values
 - “WS” include .mat files generated from data. The main folder “ValsalvaAnalyzer” includes DriverBasic.m, the core script to run the program.

When the software is downloaded, “LabChart” includes a “.mat” files for each of the eight example subjects. , and folders with results for subject 1. As datasets in “Labchart” are analyzed, output files will be stored in the respective folders.

- 1.4 Patient Data: From LabChart, export ECG, HR (derived from the ECG), and BP signals (channels 1-3) in MATLAB. Export Data (32-bit floating point), unselect *Comments* and *Event markers*. Export a representative region that includes the VM to be analyzed (we recommend including 30 seconds of data before and 30 after the VM). This file, saved as a .mat file, should be moved to the “Labchart” folder. Note that the software does not include the original LabChart files, but the example Subject1-8.mat files include exported data from characteristic patients.

Patientinfo.xls, an Excel spreadsheet (content listed in Table 1), includes patient information (age (years), sex (m/f), height (cm), weight (kg), and BMI (kg/m²)). For each subject, we list if the patient is normal weight (nw), overweight (ow) or obese (ob)²⁶, and note if the subject has a normal or pathological VM response.

- 1.6 To run the ValsalvaAnalyzer software, go to the folder ValsalvaAnalyzer and open the file DriverBasic.m in MATLAB. In the top panel click *Editor*, and then click the green triangle labeled *Run* to execute the program.

Step 2: Software platform

The software distributed via GitHub has been tested on Windows (Windows 11 Education) and Mac (MacOS Sonoma, version 14.3) and uses MATLAB (version R2023a). Defaults are set to the MacOS environment with suggestions for Windows.

- 2.1 From the pop-up menu (shown in **Fig. 2**), select software platform (PC 1 and Mac (Default) 2). Next, choose figure font size (PC 12, Mac (Default) 16), marker size (PC 10, Mac (Default) 14), and linewidth (PC 2, Mac (Default) 3).
- 2.2 Click *OK* to accept and proceed to Step 3 or click *Cancel* to end the program.

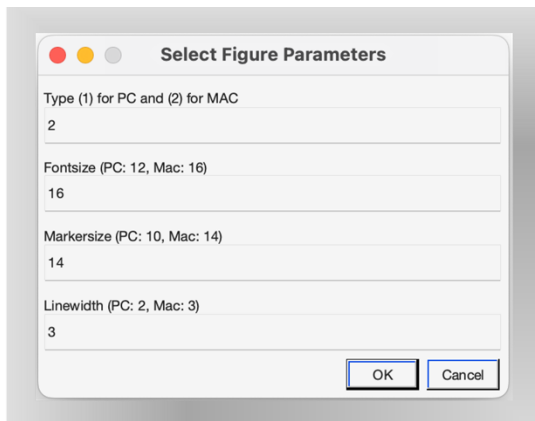


Fig. 2: Menu used to select computer type PC (1) and MAC (2, default), font (default 16), and marker (default 14) size and linewidth (default 3) used in MATLAB figures.

Step 3: Select Patients

This step involves the selection of data to be analyzed. The software will read .mat files from the folder “Labchart”. When data are exported to MATLAB, select the time-series measurements encompassing the Valsalva Maneuver (VM), including approximately 30 seconds of data before and after the VM). During this step, a menu (shown in **Fig. 3**) appears, listing the names of all subject data files. To start the analysis, the user must select patients from the menu.

- 3.1 Select one (single click), more (click holding *command* on Mac or *Control* on PC), or all (*Select all*) patients from the list for analysis. The patients in the list have the same titles as the .mat files exported from LabChart.
- 3.2 Click *OK* to proceed to Step 4 or *Cancel* to exit the program.

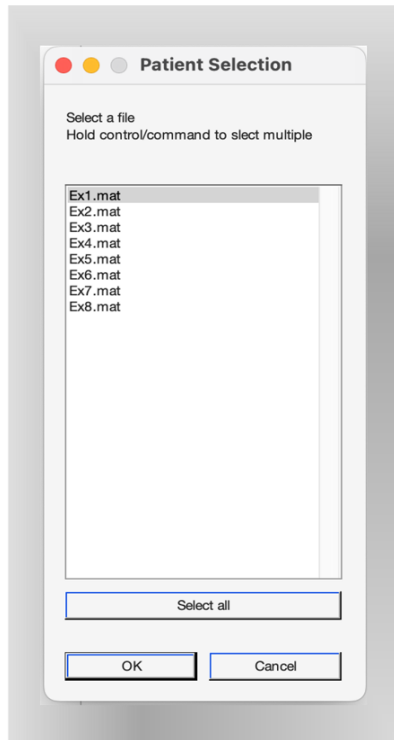


Fig. 3. Patient selection menu. Lists “.mat” files for each patient in the “Labchart” folder.

Step 4: Select Operation

The data analysis methods are listed in a menu providing available operations. These include methods for cleaning ECG and BP data, identifying VM phases, and computing VM features. The latter includes features identified from the data and outputs obtained by solving a differential equations model (outlined in Appendix A) predicting parasympathetic and sympathetic function. Computed results are saved in Figures and stored in a Table; the latter is saved as an Excel .xls file in the Markers folder. The layout of the functions within this software is illustrated in **Fig. 4**.

4.1 Select operation (options discussed below and shown in **Fig. 5**) performed on the subjects selected in Step 3. Note: operations must be run in order, and the program will repeat the selected operation for all subjects chosen in Step 3. If more than one subject and task is selected from the *Operation Selection* menu, the software will complete the first tasks for all subjects before moving on to the next task. It is advantageous to run operation 12 (summary) for all subjects.

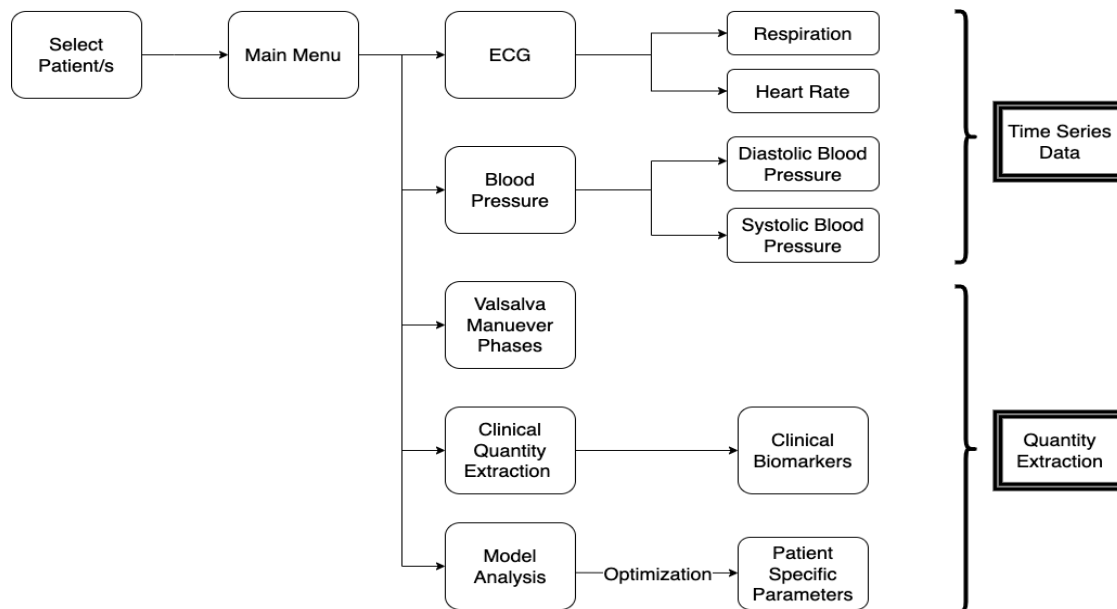


Fig. 4. Operations in the ValsalvaAnalyzer. After selecting patients, the software provides the option to correct measured signals including: (1) the ECG, from which heart rate and respiration are extracted, (2) the beat-to-beat blood pressure (BP) signal from which systolic and diastolic BP are extracted. After these procedures, the software identifies the Valsalva maneuver phases and extracts clinical biomarkers. Finally,

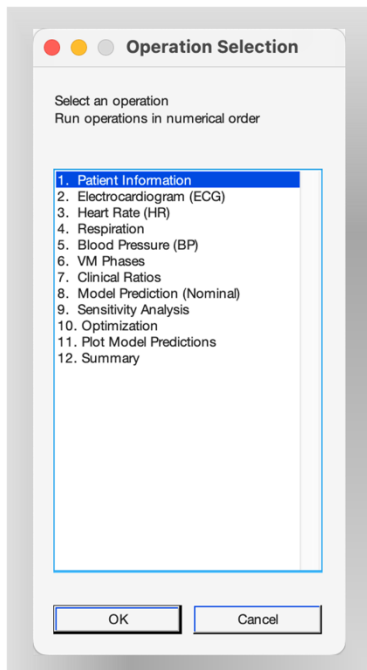


Fig. 5. Operations. Lists all tasks included in ValsalvaAnalyzer. Note, that tasks must be performed in order (from the top).

we provide the option of running a computational model predicting baroreflex function.

- 4.1.1 Patient Information (Operation 1, Step 5).
- 4.1.2 Electrocardiogram (ECG) (Operation 2, Step 6).
- 4.1.3 Heart Rate (HR) (Operation 3, Step 7).
- 4.1.4 Respiration (Operation 4, Step 8).
- 4.1.5 Blood Pressure (BP) (Operation 5, Step 9).
- 4.1.6 VM Phases (Operation 6, Step 10).
- 4.1.7 Clinical Ratios (Operation 7, Step 11).
- 4.1.8 Model Prediction (Nominal) (Operation 8, Step 12).
- 4.1.9 Sensitivity Analysis (Operation 9, Step 13).
- 4.1.10 Optimization (Operation 10, Step 14).
- 4.1.11 Plot Model Predictions (Operation 11, Step 15).
- 4.1.12 Summary (Operation 12, Step 16).

4.2 Click *OK* to proceed to the operation or click *Cancel* to return to Step 3.

Step 5. Patient Information (Operation 1)

The first operation involves inputting patient characteristics (age, sex, height, and weight) and identifying the time range over which data should be analyzed. Data should be entered in the menu shown in **Fig. 6**.

- 5.1 Enter patient *Age* (integer, years), *Sex* (m/f, male/female), *Height* (real number, cm), and *Weight* (real number, kg). Click *OK* to proceed or *Cancel* to return to Step 4. The software will run without selections. Characteristic values for the sample subjects are listed in Table 1. These values are not used in the data analysis but may be helpful for summary statistics.

Fig. 6. Patient characteristics: including Age (years), Sex (m/f), Height (cm), and Weight (kg). Note the ValsalvaAnalyzer runs if this information is left out.

- 5.2 MFigure 1 (**Fig. 7**) displays the ECG (mV) top, HR (bpm) center, and BP (mmHg) bottom panels as functions of time (seconds). Select data to analyze. Include approximately 30 seconds before and after the VM. Positioning the crosshair, click once with the mouse at the start (~30 seconds before the VM) and a second time at the end (~30 seconds after the VM). Data selected for analysis will appear in red in MFigure 1. Click *Save and Exit*.
- 5.3 MFigure 1, with the selected data, will be saved in the folder “Figures/Data” under the name “[patient name] + _dataAnalyzed.png”.

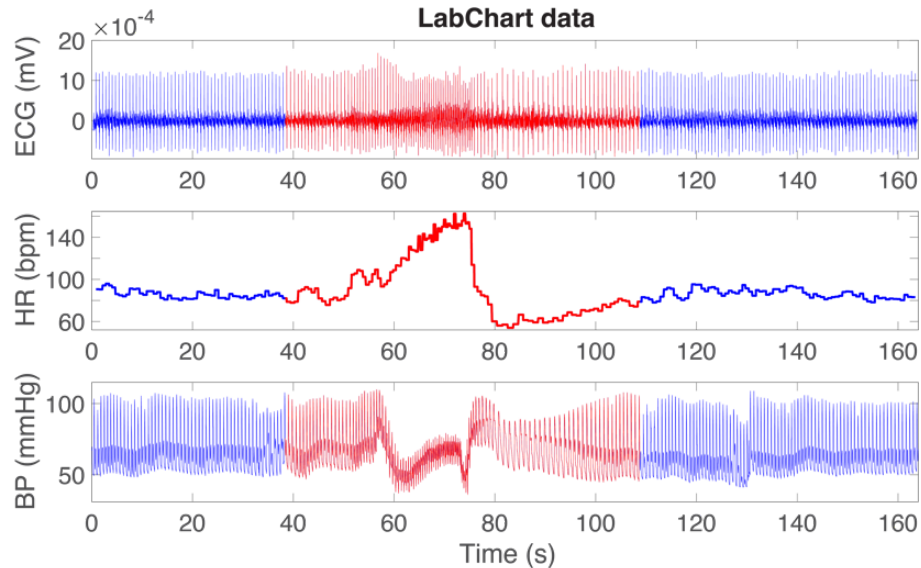


Fig. 7. Graphs depict the ECG (mV, top), heart rate (HR bpm, center), and blood pressure (mmHg, bottom) data. The blue trace shows all data stored from LabChart, and the red trace shows data selected for analysis in this study. The red region containing ECG, HR, and BP starting and ending ~20 sec before and after the VM maneuver.

Step 6. Electrocardiogram (Operation 2)

Operation 2 involves cleaning the ECG signal (removing extra and/or adding missing points). The distance between R peaks is used to generate the HR signal, and the distance between R and S peaks is used to create the respiration signal.

- 6.1 For this task, MFigure 1 (**Fig. 8(a)**) displays the ECG data (black line). R peaks are marked with red, and S peaks with blue circles. The objective of this task is to correct misplaced peaks. The total number of peaks is printed to the right of the graph. This task can only be completed if the number of R and S peaks are the same. To correct the misplaced peaks, scroll with the hand to the right through the signal and stop when the points to be corrected are in the window. An example of a misplaced S peak is shown in **Fig. 8(a)** and **Fig. 8(b)** shows the trace after the wrong S peak has been removed.

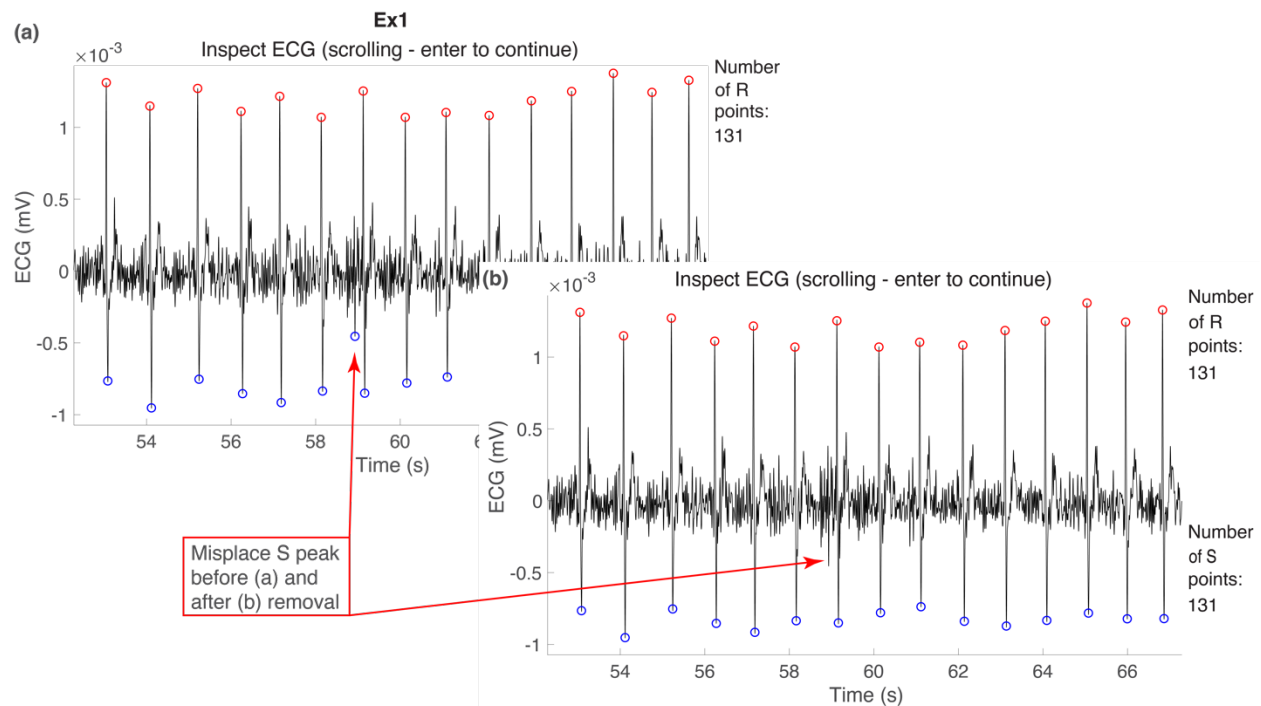


Fig. 8. Graphs used to guide ECG (mV) correction. Panel (a) shows ECG parking R and S waves. Note wrongly detected S peak. In panel (b) this S-peak has been removed. Note a clean signal will have the same number of R and S peaks, noted on the right side of the graph.

- 6.2 Correction (repeated until the number of S and R peaks are the same) involves:
 - 6.2.1 If the number of R and S peaks is equal and no points are captured incorrectly, press *Enter* on the keyboard, proceeding to Step 6.3.
 - 6.2.2 If a point (R or S) is missing, placed wrongly, or an extra point is marked, scroll to the location of the point. Press *Enter* on the keyboard, and a menu appears querying, *Do you want to correct RS points*. Click *Yes* to correct points (Step 6.2.3) and *No* to return to the operations menu (Step 4).
 - 6.2.3 A menu appears: *Click on point to correct*. Press *OK*, place the crosshair, and click on the point to correct. The next menu queries *Add or remove point*. Options are *Add* (Task 6.2.4), *Remove* (Task 6.2.5), or *Cancel* returning to Step 6.2.2.
 - 6.2.4 The point marked will be added and appear in red (R peak) or blue (S peak). Note: The program will use the exact location of the click and automatically classify the point as R or S.
 - 6.2.5 The point marked will be removed. If the point does not disappear, repeat this step, returning to task 6.2.2.
- 6.3 Repeat Step 6.2 until all R and S peaks are identified correctly, and the number of R and S peaks are the same. Then press *Enter* on the keyboard. On the prompt asking to correct

points, click *No*. Return to Step 4. Note: If the time series has no apparent errors, but the number of R and S peaks is not identical, a start or end peak is likely missing. To correct this error, return to Step 6.2.

- 6.4 If you click *No* when in the menu *Do you want to correct RS points* and the number of R and S peaks is not identical, a new menu pops up, noting that the number of R and S peaks differ. After clicking *OK*, the code returns to Step 6.2.

Step 7. HR (Operation 3)

This step involves converting the RR intervals to HR. After the ECG has been corrected (as described above), the HR signal is smooth for most datasets. However, in some datasets, the HR signal might not be smooth due to artifacts (see **Fig. 9(a)**). Operation 3 provides the opportunity to smooth the HR signal, as illustrated in **Fig. 8(b)**.

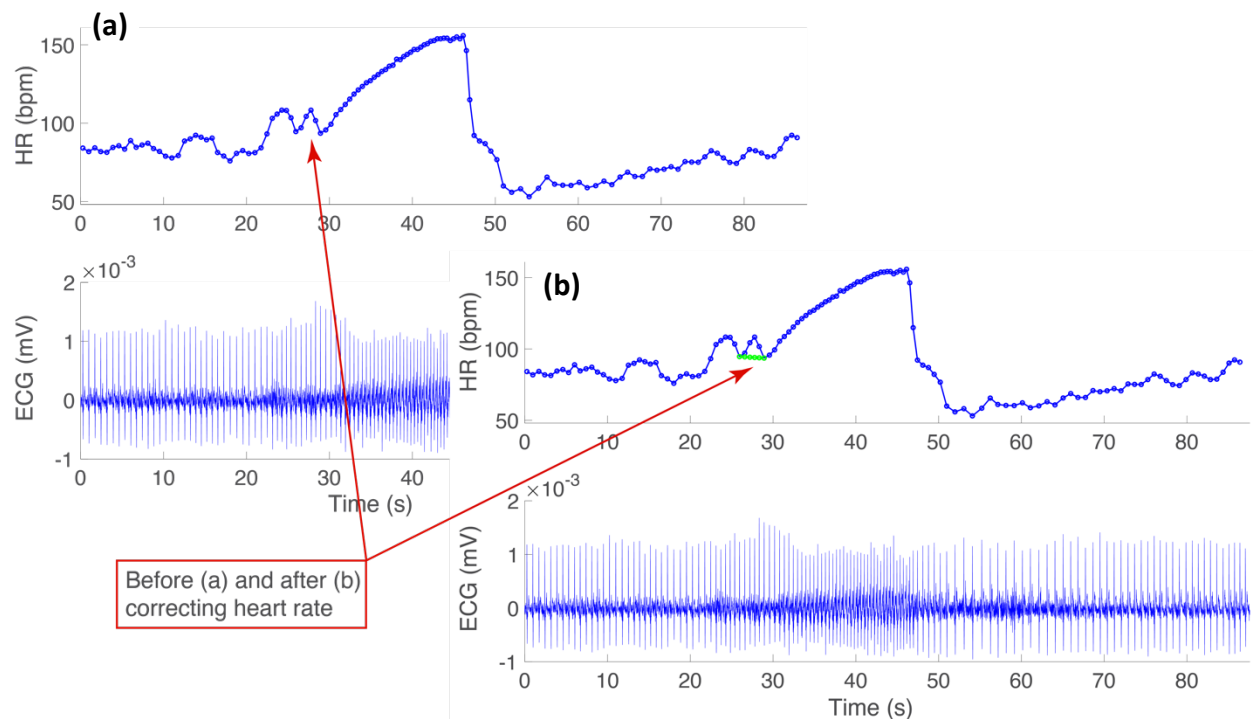


Fig. 9. Graphs used to guide heart rate (HR, bpm) correction. Panel (a) shows the heart rate generated from the corrected ECG. Panel (b) shows an example of a spline connecting two points removing an artifact from the heart rate signal.

- 7.1 MFigure 1 (**Fig. 9(a)**) displays HR (bpm) in the top panel. It is computed from the corrected ECG. The raw ECG (mV) signal is shown in the bottom panel. If the HR signal does not have artifacts, click *Save and Exit*, returning to Step 4. If there are errors in the data (compare **Fig. 9(a)** and **(b)**), click *Correct Heart Rate* and proceed to Step 7.2.

- 7.2 Use the hand to scroll along the time series and locate artifacts. Press *Enter* on the keyboard when viewing a region to correct. Proceed to Step 7.3.
- 7.3 Click *OK* on the menu querying *Click at points to correct*. Align the crosshair over the first point before the artifact and click once with the mouse. Align the crosshair over the first point after the artifact and click a second time with the mouse. A linear spline (plotted in green) connects the two points. A menu asks, *Accept change?* Answers: *Yes* (proceed to Step 7.4.1), *Undo* (go to Step 7.4.2), and *Add change* (go to Step 7.4.3).
 - 7.4.1 *Yes* accepts the linear spline, exits this operation, and returns to Step 4.
 - 7.4.2 *Undo* removes the linear spline and returns to Step 7.2.
 - 7.4.3 *Add* keeps the linear spline and returns to Step 7.2 to allow additional corrections.
- 7.4 MFigure 1 displays the HR (bpm) in the top panel and ECG (mV) bottom panel. The data will be saved in the folder “Figures/Data” under the name “[patient name] + _HeartRateECG.png”. To continue, press *Save and Exit*.

Step 8. Respiration (Operation 4)

A respiration signal is extracted from the corrected ECG signal by computing the difference between R and S peaks, fitting a spline through this difference as described in the study by Randall et al.²⁰ In this version of the software, the signal is displayed, but cannot be corrected or cleaned.

- 8.1 MFigure 1 (**Fig. 10**) depicts the respiratory signal extracted from the difference between the corrected R and S peaks. Inspect the graph, click *Save and Exit*, returning to Step 4.
- 8.2 MFigure 1 will be saved in the folder “Figures/Data” under the name “[patient name] + _RespiratorySignal.png”.

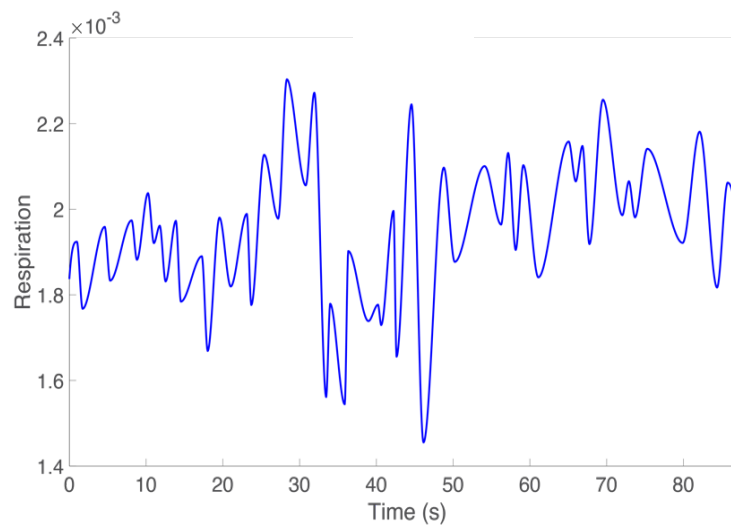


Fig. 10. The respiratory signal is generated from the R-S interval as described by Randall et al.⁵

Step 9. Blood Pressure (Operation 5)

This step involves extracting systolic and diastolic BP over time. The two curves are formed by generating a spline through selected data points. For this operation, the user can correct automatically detected curves. Given the significant change in BP, correction is likely needed immediately following the end of the breath-hold.



Fig. 11. Blood pressure correction. (a) click on two consecutive peaks (marker by *) to determine the average length of the cardiac cycle. (b) example showing original and corrected systolic (red) and diastolic (green) pressure. (c) the original and corrected systolic and diastolic blood pressure signals.

- 9.1 MFigure 1 (shown in **Fig. 11(a)**) displays a zoomed window with the BP data. The user should align the crosshair with a BP peak and click once with the mouse. Then, align the crosshair on the next peak to the right and click again. The ValsalvaAnalyzer uses the distance between the two peaks to estimate the cardiac cycle length. This distance is needed to identify systolic and diastolic peaks. MFigure 2 (shown in **Fig. 11(b-c)**) appears, displaying automatically detected systolic and diastolic signals.
- 9.2 Systolic BP correction. A menu prompts: *Do you want to correct systolic points?* Answer Yes (Step 9.4) initiates systolic BP correction, and No (Step 9.3) proceeds diastolic BP correction.

- 9.3 Diastolic BP correction starts with a menu querying: *Do you want to correct diastolic points?* The answer *Yes* (Step 9.4) initiates a protocol for correcting the diastolic BP, and *No* completes the corrections. A button providing the option to *Save and Exit*, and the ValsalvaAnalyzer returns to Step 4. Note that the protocol for correcting diastolic BP is identical to the one correcting systolic BP; both are described in 9.4.
- 9.4 MFigure 2 shows a zoom of the first 40-second data. Inspect the region and keep scrolling, using the hand, until a wrong point appears (compare **Fig. 11(a)** and **(b)**). Press *Enter* on the keyboard and click on the last correct peak before the misplaced point(s), then click on all points to be included, ending with a correct point. Press *Enter* when finished. Correction can be repeated until no more segments need to be modified. For each section, the corrected points are connected with a red (SBP) and green (DBP) dotted line attached to existing points at each end. The continuous BP signal, plotted in blue, is used as a guide. The system will record peaks clicked even if they do not align with the BP signal. This operation corrects the systolic and diastolic signals. Within each signal, only correct points associated with the signal, i.e., do not try to correct diastolic points when correcting the systolic BP or vice versa.

Step 10. Valsalva Maneuver (VM) Phases (Operation 6)

Operation 6 starts by identifying the VM phases and assumes a characteristic hemodynamic response to the VM. However, the user can manually select VM phases capturing abnormal hemodynamic responses not readily identified by the software. The breath-hold start is marked by the lowest BP value before the first peak, and the end is marked by the BP value before the second BP drop. After identifying these points, the software determines the four VM phases from the characteristics of the signals.

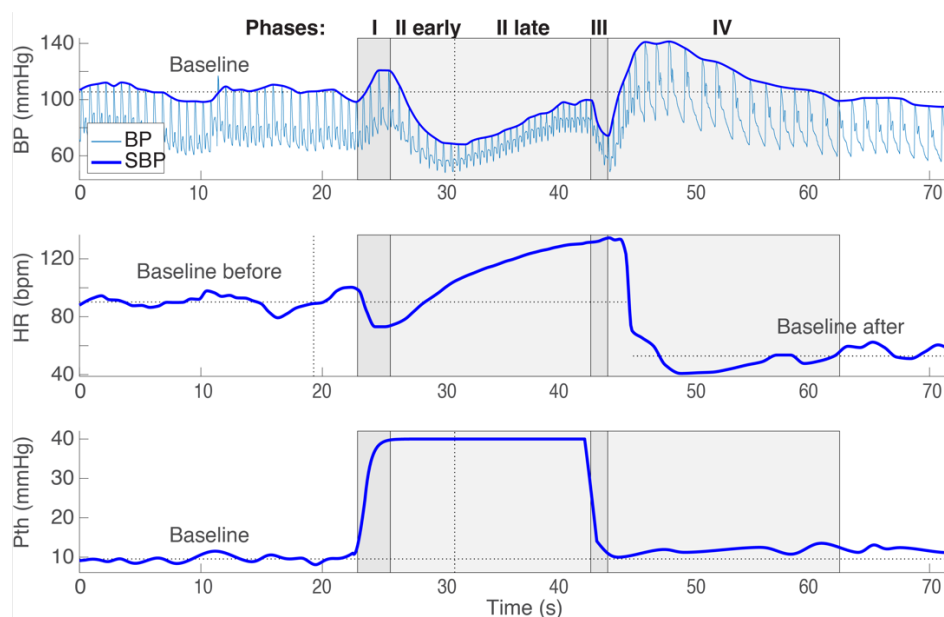


Fig. 12. Valsalva phases. The top graph shows blood pressure and systemic blood pressure, the second panel shows heart rate, and the bottom panel thoracic pressure. The latter is obtained by merging the respiratory signal with pressure during breath-hold (set to 40 mmHg). The Valsalva phases are marked with gray panels. The baseline (mean value) for each signal is denoted by a horizontal dashed line.

- 10.1 MFigure 1 (shown in **Fig. 12**) depicts continuous BP (thin line) and systolic BP (SBP, bold line) BP in the top panel (mmHg), HR (bpm) in the 2nd panel, respiration (Resp, mV) in the bottom panel, and ECG (mV) in the bottom panel. To mark the VM start, align the crosshair with the breath-hold onset (the SBP minimum immediately before the significant SBP rise and HR decrease) and click once with the mouse. Then, to mark the VM end, align the crosshair with the breath-hold end (the BP value immediately before the 2nd SBP drop) and click once with the mouse. The ValsalvaAnalyzer uses these points to determine the four VM phases depicted in MFigure 2, displaying BP (mmHg) in the top panel, HR (bpm) in the center panel, and respiration (Resp, mV) in the bottom panel in **Fig. 12**.
- 10.2 A menu queries: *Accept indices?* Answer *Yes* complete the operation, and then return to Step 4. Answer *No* provides the opportunity to inspect the automated detection of phases delineated by vertical lines. A menu queries: *Index Correction*. Select one (single click), multiple (hold *command* on Mac, *control* on PC), or all (click *Select all*), then click *OK* (proceeding to Step 10.3 for correction), or *Cancel*, returning to Step 10.1.
- 10.3 A crosshair appears in MFigure 2. The second line of the title denotes the phase being corrected. For the selected phase, click the correct time, marking the onset of the phase. This operation is repeated until all selected phases have been corrected. The menu will reappear at this point, querying: *Accept indices?* (Reverting to Step 10.1). Note: Phases must be clicked in the correct order.
- 10.4 MFigure 3 (**Fig. 12**) displays the BP (mmHg) top panel, HR (bpm) center panel, and thoracic pressure (Pth, mmHg) bottom panel. The four phases are shaded in gray. Click *Save and Exit* to continue (reverting to Step 4). This figure will be saved in the folder “Figures/Data” under the name “[patient name] + _VMphases.png”.

Step 11. Clinical Ratios (Operation 7)

This step computes clinical ratios characterizing the Valsalva Maneuver (VM). All factors are listed in **Table 2**. These include patient characteristics (patient ID, age, sex, height, and weight), duration of each VM phase, characteristic minimum and maximum BP, HR, RR intervals within each VM phase^{27,28}, and pressure recovery time^{29,30}. We also compute slopes of HR and RR regression lines in early phase II (cyan line) and IV (brown line) characterizing vagal stimulation as well as pressure increase in early (cyan line) and late (blue line) phase II and early phase IV (brown line) characterizing sympathetic stimulation. In addition, the ValsalvaAnalyzer characterizes the change in SBP and vagal^{1,29,31,32} and adrenergic^{1,29,30,33} markers. Again, the automatically detected phases and points can be corrected as needed. For example, the maximum BP and minimum HR in early phase IV are often misaligned. **Fig. 13** depicts the clinical ratios before (a) and after (b) correction and **Fig. 14** depicts the ratios adapted from Palamachuck et al.¹ and Sandroni et al.²⁸. Note quantities displayed in this figure are derived from the values extracted from the data as described in 11.1-11.4.

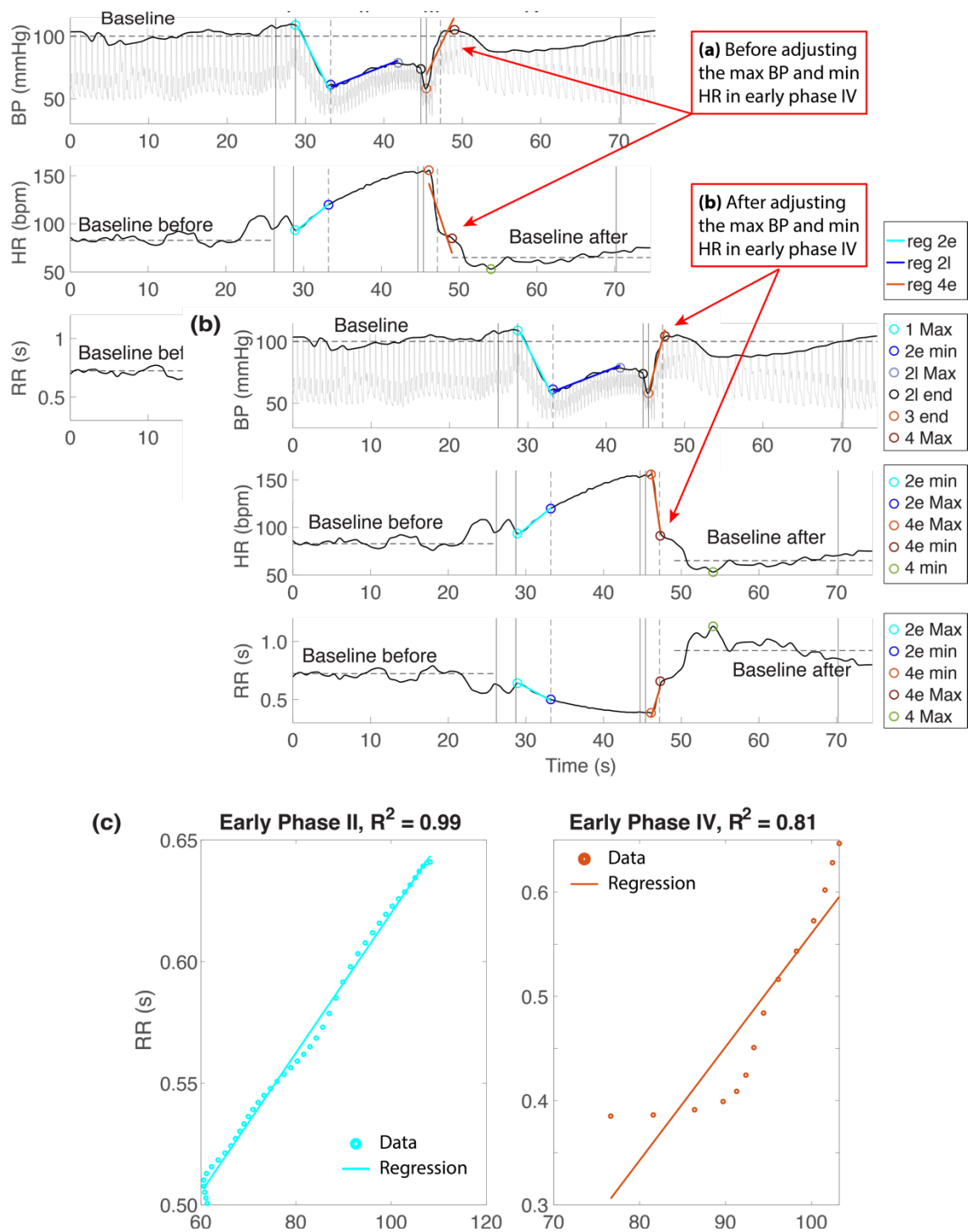


Fig. 13. Clinical ratios. Panels (a) and (b) show ratios and regression lines for blood pressure (BP, mmHg) top panel, heart rate (HR, bpm) center panel, and the RR interval (s) bottom panel. (a) Shows the automatically detected ratios and (b) shows corrected maximum BP and minimum HR in early phase IV. Panel (c) shows the regression line through corrected ratios.

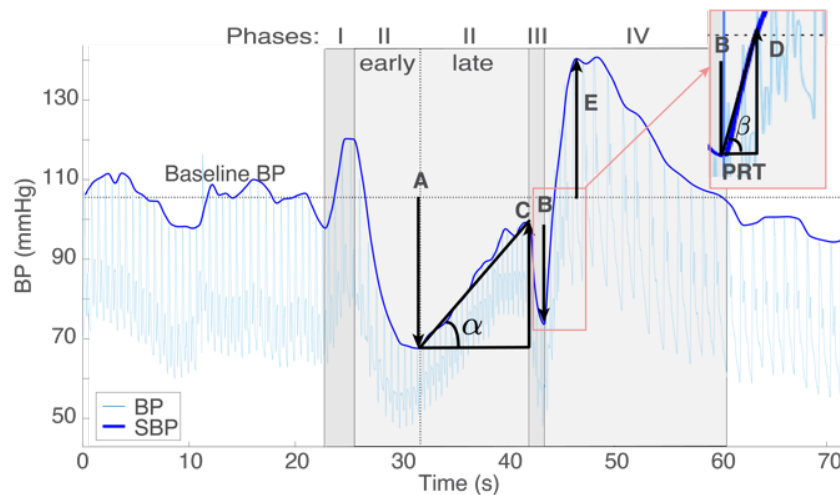


Fig. 14. Clinical Blood pressure ratios from Palamachuck¹.

- 11.1 MFigure 1 (shown in **Fig. 13(a,b)**) depicts systolic BP (SBP, mmHg) in the top panel, HR (bpm) in the center panel, and the RR interval (s) in the bottom panel. Characteristic SBP, HR, and RR values are annotated with circular markers. A menu appears, querying, “Do you want to accept markers?”. Inspect the markers. Click Yes if all points are correct; this operation is completed, reverting to Step 4. Click No if a point needs to be adjusted.
- 11.2 A menu appears, querying: *Select points to move*. The menu enables the selection of one (single click), multiple (hold *command* on Mac, *control* on PC), or all (click *Select all*) points.
- 11.2 If indices have been selected, click *OK* to continue (Step 11.3) or click *Cancel* to proceed without changing any indices, continuing to Step 11.4.
- 11.3 A pop-up menu lists the points to be corrected for each selected quantity. Click *OK* to continue. Align the crosshair at the desired point and click once with the mouse. When all selected points have been corrected, the ValsalvaAnalyzer continues to Step 11.4. To continue, press *Save and Exit*.
- 11.4 MFigure 1 displays BP (mmHg) in the top panel, HR (bpm) in the center panel, and RR intervals (s) in the bottom panel. Corrected points and regression lines during early and late phase II and early phase IV. After inspecting the graph, MFigure 2 (shown in **Fig. 13(c)**) displays the regression lines relating the RR interval to the SBP and the R^2 value. Press *Save and Exit* on MFigure 1, returning to Step 4. MFigures 1 and 2 will be saved in the folder “Figures/Data” under the names “[patient name] + ratios.png” and “[patient name] + _ratios_regression.png”.

Step 12. Run Model (Operation 8)

Operation 8 involves solving the baroreflex differential equations model from Randall et al.²⁰, which predicts sympathetic and parasympathetic signaling. This step runs the model with parameter values set using patient information and clinical ratios identified in Operation 10. This operation is needed to test nominal predictions; if not, results from the optimization operation (Step 14) may not be successful for the specific dataset.

12.1 Solves the differential equations model by Randell et al.²⁰ using nominal patient-specific parameter values extracted from the data and the patient information entered in Step 5. MFigure 1 depicts BP (mmHg) top left panel, HR (bpm) data (blue) and model (magenta) top right panel, thoracic pressure (Pth, mmHg) bottom left panel, and parasympathetic (magenta) and sympathetic (dark purple) predictions bottom right panel. Click *Save and Exit* to proceed, returning to Step 4. This figure will be saved in the folder “Figures/Model_fits” as “[patient name] + _nominal.png”.

Step 13. Sensitivity Analysis (Operation 9)

Sensitivity analysis is not required for the data analysis. This analysis generates a graph depicting model parameters' sensitivity (or importance) for accurate HR prediction. The operation uses local sensitivity analysis described in detail by Randall et al.²⁰

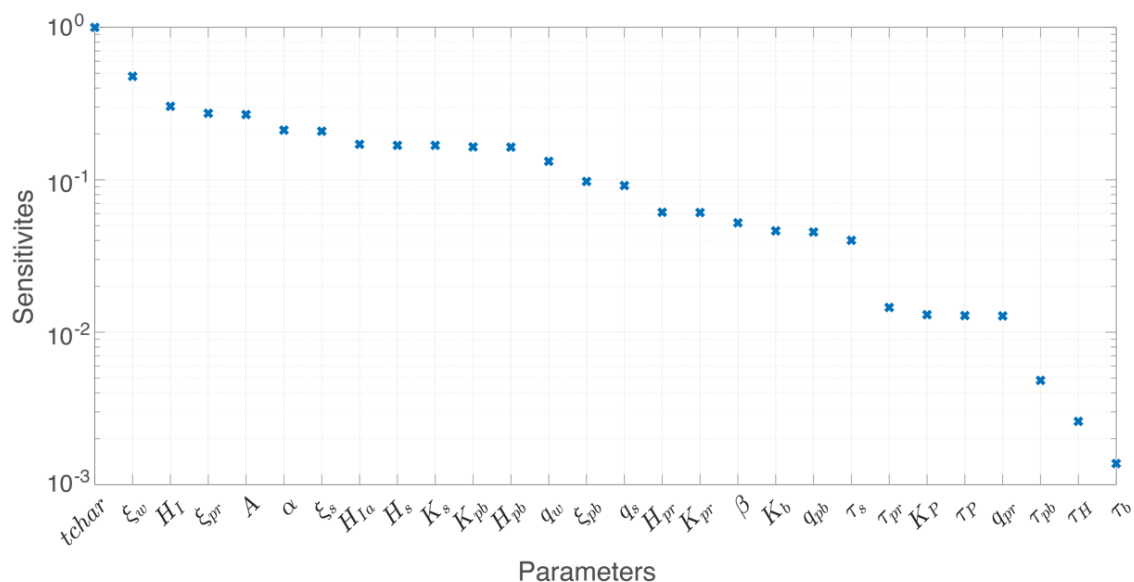


Fig. 15. Sensitivity of model parameters to prediction of heart rate. The model is described in detail in the study by Randel et al.⁵, and parameters are explained in Tables 2 (estimated and patient specific parameters) and Table A1 (parameters that are fixed for all patients).

13.1 This operation computes the sensitivity of model parameters to HR. Results (on a log scale) depicting ranked sensitivities are shown in MFigure 1 (**Fig. 15**). Click *Save and exit*

to proceed, returning to Step 4. Note that this computation takes a few minutes. The result shown in MFigure 1 is saved in the folder “Figures/Model_fits” as “[patient name] + _sensitivities.png”.

Step 14. Optimization (Operation 10)

This operation estimates a subset of identifiable parameters given the mathematical differential equations model and data availability (HR). The outcome is an HR model calibrated to data. In addition to a set of estimated parameters, the optimized model predicts sympathetic and parasympathetic signaling. If the simulation does not fit the data well, the predicted sympathetic and parasympathetic signaling cannot be interpreted. Optimization is conducted using the Levenberg Marquardt method as described by Randall et al.²⁰

- 14.1 Estimates parameters calibrating the patient-specific model to HR data. This operation can take 5-10 minutes to complete. During computation, the MATLAB command window prints up to 30 lines of five numbers denoting (from left to right) the gradient norm, the least squares cost, the iteration number, and the Jacobian matrix condition number. When the optimization is complete, the ValsalvaAnalyzer returns to Step 4. The estimated parameter and a vector *INDMAP* are saved in the folder “Optimized”.

5. Plot Model Predictions (Operation 11)

Results of model predictions with nominal (Step 12, Operation 8) and estimated (Step 14, Operation 10) parameter values are plotted. If the HR prediction shown in the top right panel of MFigure 1 is reasonable, the code predicts sympathetic and parasympathetic signaling (Bottom right panel of MFigure 1).

- 15.1 On the menu *View Model Predictions*, click *Nominal* to plot the model predictions from Step 12 or *Optimized* to view the optimized model predictions from Step 14. MFigure 1 (shown in **Fig. 16**, nominal (a) and optimized (b)) depicts BP (mmHg) in the top left corner, HR (bpm) in the top right corner data (blue), and the model (magenta), the thoracic pressure (Pth, mmHg) is at the bottom left corner, and the parasympathetic (magenta) and sympathetic (dark purple) predictions are in the bottom right corner. Click *Save and exit* to proceed, returning to Step 4. This figure will be saved in the folder “Figures/Model_fits” under the name “[patient name] + _[action].png”, where [action=nominal] or [action=optimal] depending on chosen action.

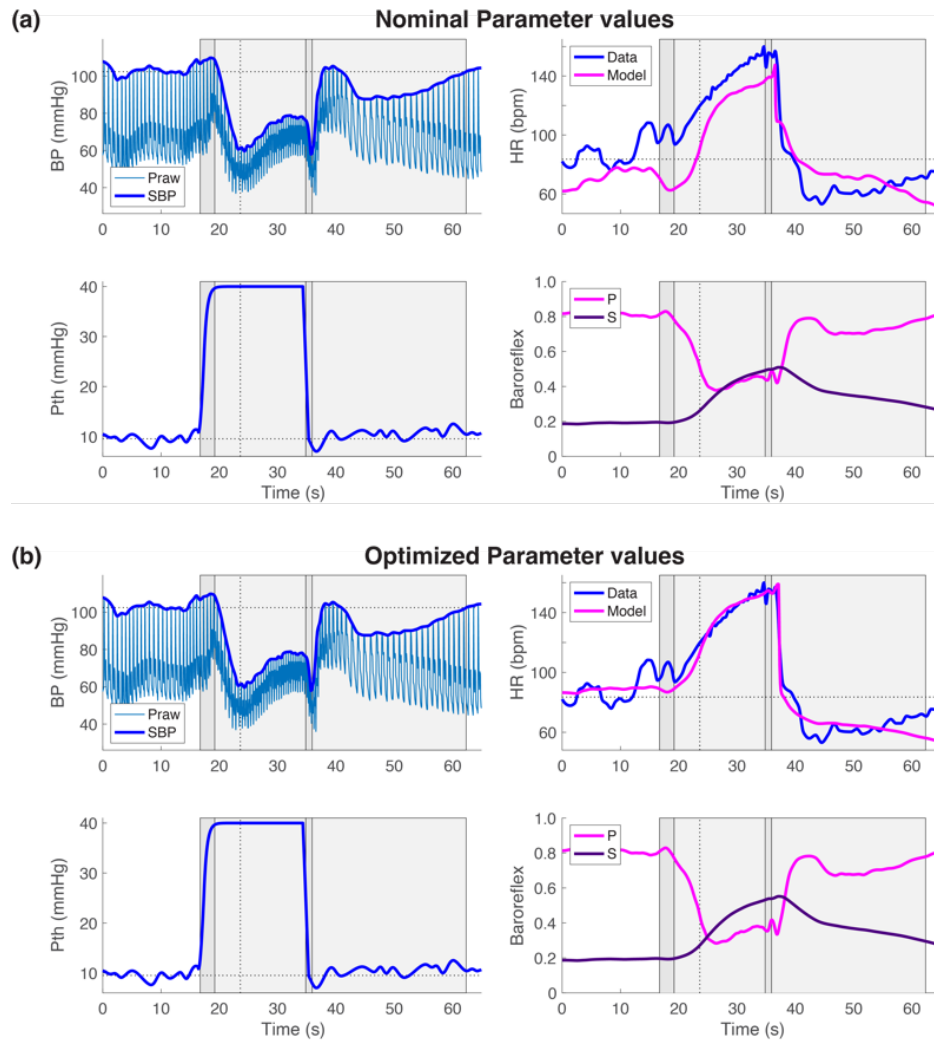


Fig. 16. Model prediction with nominal (automatically computed) (a) and optimized (b) parameter values. The figure shows top left: blood pressure (systolic (SBP) and time-varying (BP), mmHg); top right heart rate (HR, bpm), model prediction (pink line), data (blue line); bottom left thoracic pressure (Pth, mmHg), and predictions of parasympathetic (pink) and sympathetic (purple) activity. Both are non-dimensional.

Step 16. Summary (Operation 12)

16.1 A summary of findings is stored in an Excel spreadsheet. On the menu, *Save Data*, enter the preferred sheet name into the textbox with the file extension .xlsx. If the spreadsheet exists, a menu queries if you want to *Add or Overwrite* the existing sheet. This operation also prints outputs to the MATLAB command line. Click *OK* to generate the Excel sheet and *Cancel* to only output to the MATLAB Command Line. The saved Excel file contains patient information (Step 5), Clinical Markers and Regression Lines (Step 11), and Nominal (or Optimized) parameter values (Steps 12 and 14).

Limitations

The ValsalvaAnalyzer software has a few limitations. If the code is disrupted before a task is completed, the program may exit within a folder other than the main folder. In this case, returning to the main directory is essential before completing the analysis. For example, the code could crash in the “Core” folder, and to return, either type `cd ..` on the command line or use the mouse to return to the correct folder. The software has two model limitations. First, it is not possible to alter the respiration signal, which is extracted directly from the RS peaks. Second, the optimization operation estimates a fixed set of parameters. This set can be modeled by changing indices in `model_opt.m` located in the Core directory. However, it should be noted that in addition to the estimated parameters, some are patient-specific. A detailed discussion of model parameters and their impact can be found in the study by Randall et al.²⁰ All estimated and patient-specific parameters and quantitative clinical markers are saved in the Excel sheet stored as part of the Summary Operation.