A Cardiovascular Simulator for Research

User's Manual and Software Guide

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1 Introduction

Computational modeling and simulation studies can facilitate the advancement of cardiovascular research by complementing experimental studies. Through computational studies, the researcher may formulate hypotheses which may be subsequently tested through experimental studies or the researcher may develop and evaluate inverse modeling algorithms for determining important cardiovascular parameters from experimental data. Experimental studies, in turn, permit the researcher to construct more accurate computational models thereby improving the researcher's understanding of the cardiovascular system and ability to devise new experimental hypotheses and inverse modeling algorithms.

The general aim of this document is to introduce the Research CardioVascular SIMulator (*RCVSIM*) software which may be downloaded from PhysioNet (*www.physionet.org*) – an NIH-funded national research resource that provides well characterized, experimental data sets and open-source software for their analysis. *RCVSIM* is capable of generating reasonable human pulsatile hemodynamic waveforms, cardiac function and venous return curves, and beat-to-beat hemodynamic variability. The data simulated by *RCVSIM* is written in a format which is identical to the experimental data sets. As such, the open-source data analysis software may be readily applied to the simulated data as well. The data generated by *RCVSIM* may be viewed as they are being calculated (on-line viewing) or any time after they have been calculated (off-line viewing) with the WAVE display system (which is also provided by PhysioNet) and Gnuplot. The *RCVSIM* software is open-source and extensively commented and includes Linux binaries that may be executed at the Linux or MATLAB prompts. It should also be possible to compile the source code to create binaries that may be executed on Unix platforms (*e.g.*, Solaris, SunOS). (Note that MATLAB is required for compiling the source code.) *RCVSIM* has been previously employed in cardiovascular research for the development and evaluation of system identification methods aimed at the dynamical characterization of autonomic regulatory mechanisms [**?**, 4, 8].

This document specifically explains how to install and use the *RCVSIM* software and describes the open-source code and each of its functions so that *RCVSIM* may be easily extended and modified by the researcher to achieve his desired research objective. In Section 2, a brief description of the components and parameters of the human cardiovascular model is given. (A detailed description may be found in [?, 4, 7].) In Section 3, a description of the source code and an explanation of how to alter it are provided. In Section 4, detailed instructions on software installation and compilation are outlined. In Section 5, instructions on software execution, including many examples, are given. Finally, in Section 6, an example illustrating how the software may be utilized in cardiovascular research is provided. Note that if the researcher is interested in executing the software but not editing it, then he may skip Section 3 without loss of continuity.

2 Human Cardiovascular Model

The human cardiovascular model upon which *RCVSIM* is based includes three major components. The first component is a lumped parameter model of the pulsatile heart and circulation which may be implemented as an intact preparation, a heart-lung unit preparation designed for measuring cardiac function curves, or a systemic circulation preparation designed for measuring venous return curves. The second component is a short-term regulatory system model which includes an arterial

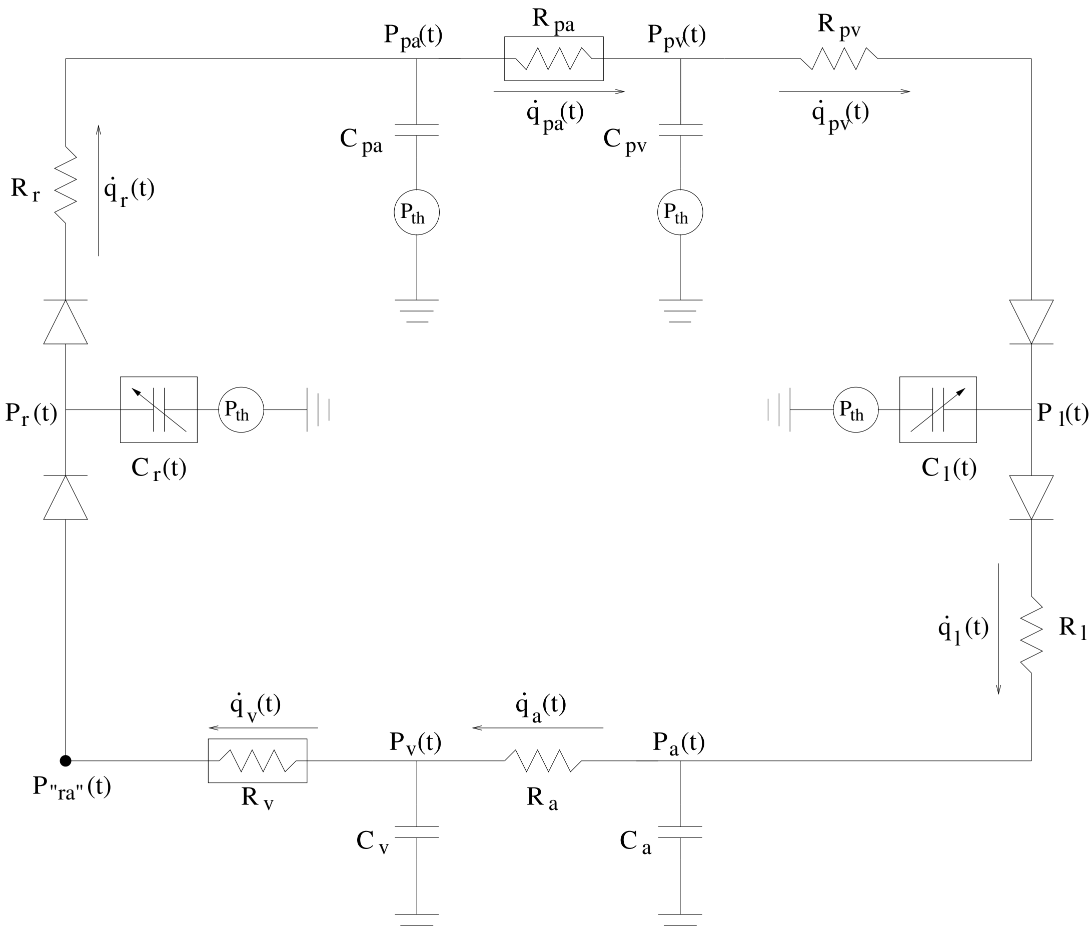


Figure 1: Electrical circuit analog of the intact human pulsatile heart and circulation. Each box encompassing a circuit element denotes a nonlinear element.

baroreflex system, a cardiopulmonary baroreflex system, and a direct neural coupling mechanism between respiration and heart rate. The final component is a model of resting physiologic perturbations which includes respiration, autoregulation of local vascular beds (exogenous disturbance to systemic arterial resistance), and higher brain center activity impinging on the autonomic nervous system(*1/f* exogenous disturbance to heart rate).

2.1 Pulsatile Heart and Circulation

The lumped parameter model of the intact pulsatile heart and circulation is illustrated in Figure 1 in terms of its electrical circuit analog. Here, charge is analogous to blood volume (Q, ml), current, to blood flow rate ($\dot{q}$, ml/s), and voltage, to pressure (P, mmHg). The model consists of six compartments which represent the left and right ventricles (l, r), systemic arteries and veins (a, v), and pulmonary arteries and veins (pa, pv). Each compartment consists of a conduit for viscous blood flow with resistance (R) and a volume storage element with compliance (C) and unstressed

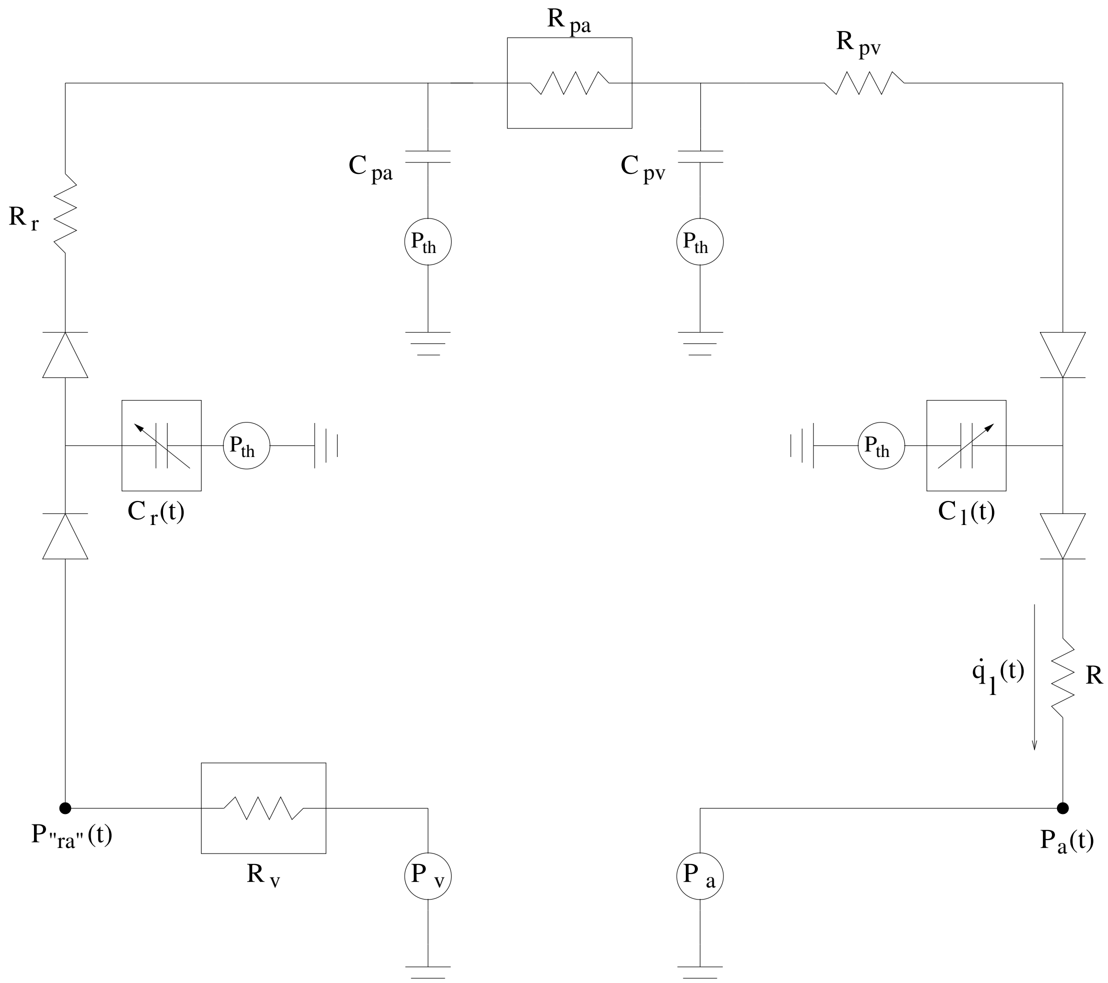


Figure 2: Electrical circuit analog of the human heart-lung unit preparation designed for measuring cardiac function curves. Each box encompassing a circuit element denotes a nonlinear element.

volume (Q^0). Two of the resistances and two of the compliances are nonlinear. The systemic venous resistance is represented by a Starling resistor (with chamber pressure set to atmospheric pressure), while the pulmonary arterial resistance is represented by an infinite number of parallel Starling resistors (with chamber pressure equal to alveolar (alv) pressure), arranged vertically, one on top of the other. The pressure-volume relationships of the left and right ventricles consist of an essentially linear regime (characterized by compliance and unstressed volume), a diastolic volume limit (Q^{max}), and a systolic pressure limit (P^{max}). The compliances of the linear regime of the ventricular pressure-volume relationship vary periodically over time (time evolution is precisely determined by the end-diastolic compliance (ed), the end-systolic (es) compliance, and the heart rate (F)) and are responsible for driving the flow of blood. The four ideal diodes represent the ventricular inflow and outflow valves and ensure uni-directional blood flow. Finally, the reference pressure is set to intrathoracic (th) pressure for the ventricular and pulmonary compartments.

Figure 2 illustrates the electrical circuit analog of the lumped parameter model of the human heart-lung unit preparation. The input pressure to the heart-lung unit here is defined to be the

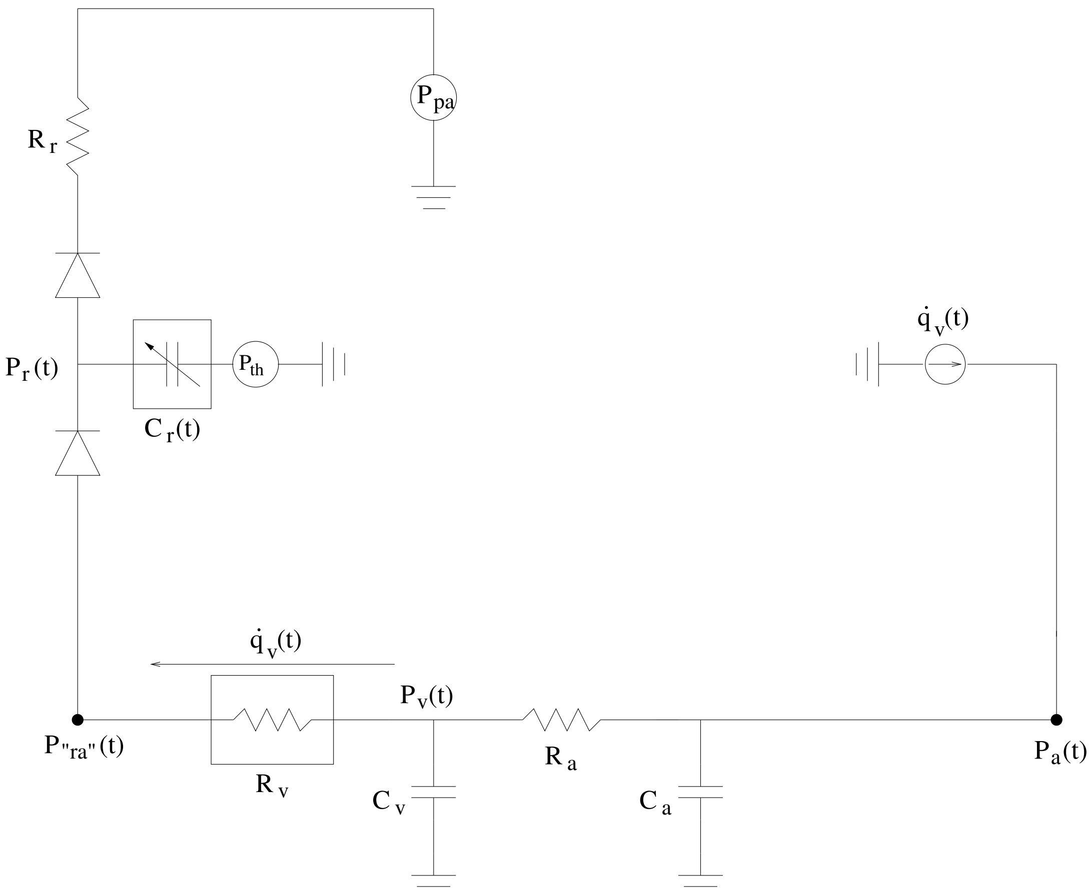


Figure 3: Electrical circuit analog of the human systemic circulation preparation designed for measuring venous return curves. Each box encompassing a circuit element denotes a nonlinear element.

node labelled $P_{“ra”}(t)$ – the location of where the right atrium would be if it were explicitly included in the model. Cardiac function curves may be obtained from this preparation by varying the independent voltage sources, P_a and P_v, and time-averaging the resulting $\dot{q}_l(t)$ and $P_{“ra”}(t)$.

Figure 3 illustrates the electrical circuit analog of the lumped parameter model of the human systemic circulation preparation. Venous return curves may be measured from this preparation by adjusting the value of $C_r(t)$ at end-diastole (C_r^{ed}) in order to vary $P_{“ra”}(t)$ – the pressure that impedes flow into the right ventricle – and time-averaging the resulting $\dot{q}_v(t)$ and $P_{“ra”}(t)$. Note that the independent current source here ($\dot{q}_v(t)$) keeps the mean systemic (ms) pressure precisely constant throughout the measurement period by pumping into the systemic circulation whatever is pumped out.

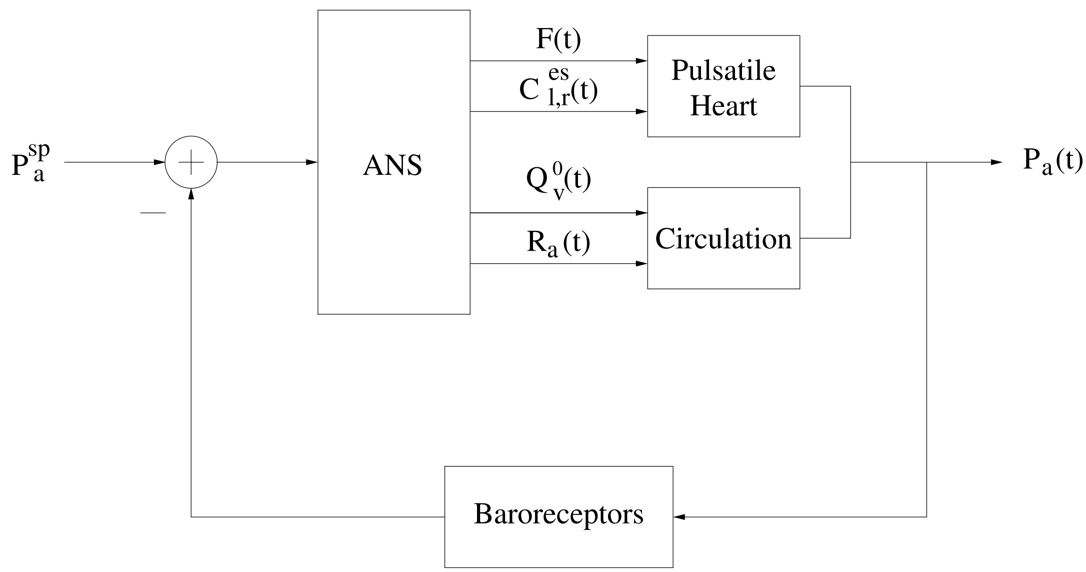


Figure 4: Block diagram of the feedback system depicting the arterial baroreflex arc.

2.2 Short-Term Regulatory System

The arterial baroreflex arc is implemented according to the feedback system illustrated in Figure 4. This system is aimed at tracking a setpoint (sp) pressure through the following sequence of events. The baroreceptors sense $P_a(t)$ and relay this pressure to the autonomic nervous system (ANS). The ANS compares the deviation between the sensed pressure and P_a^{sp} with zero and then responds by adjusting four parameters of the pulsatile heart and circulation in order to keep the ensuing $P_a(t)$ near P_a^{sp}. The four adjustable parameters are $F(t)$, $C_{l,r}(t)$ at end-systole ($C_{l,r}^{es}(t)$), $Q_v^0(t)$, and $R_a(t)$. The ANS controls these parameters based on the history of $P_a(t) - P_a^{sp}$ specifically according to the following nonlinear, dynamical mapping:

$$ap(t) = \int (G_p p(\tau) + G_s s(\tau)) S \arctan\left(\frac{P_a(t-\tau) - P_a^{sp}}{S}\right) d\tau + ap^{sp}, \tag{1}$$

where ap may represent any of the four adjustable parameters, the arctan function (which is parametrized by the constant S) imposes arterial baroreflex saturation, $p(t)$ and $s(t)$ are unit-area effector mechanisms which respectively represent the fast, parasympathetic limb of the ANS and the slower, sympathetic limb (both α- and β-sympathetic sublimbs; see Figure 5), and G_p and G_s reflect the respective static gain values of the effector mechanisms. Note that in order to map $F(t)$ to the times of onset of ventricular contraction (which amounts to re-initiating the variable, ventricular compliance time evolution), an "integrate and fire" model of the sinoatrial node is incorporated in the model.

The cardiopulmonary baroreflex arc is also implemented according to a feedback diagram analogous to Figure 4. However, the sensed pressure here is defined to be the effective right atrial transmural pressure ($P_{``ra"}^{tr}(t) = P_{``ra"}(t) - P_{th}(t)$) of the pulsatile heart and circulation model.

The direct neural coupling mechanism between respiration and heart rate is characterized by

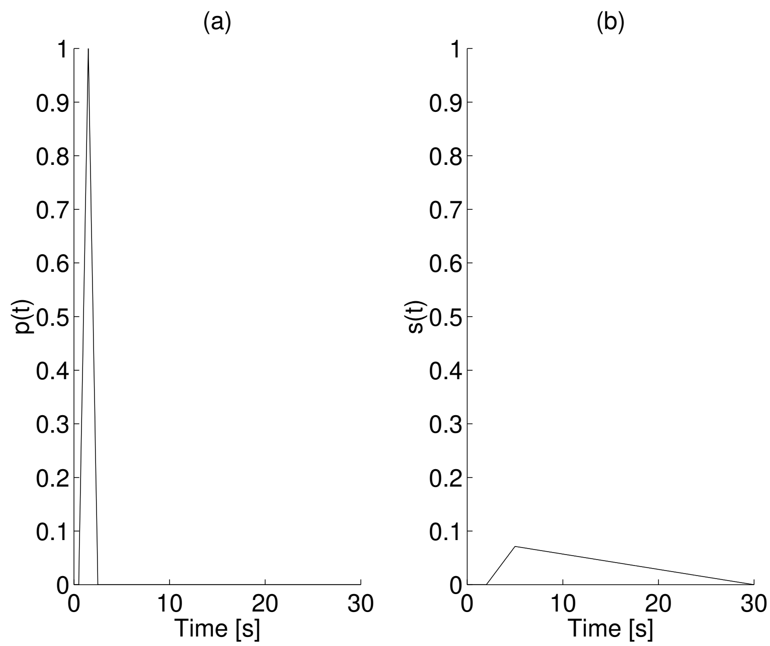


Figure 5: Unit-area effector mechanisms representing (a) the fast, parasympathetic limb $p(t)$ and (b) the slower, sympathetic limb $s(t)$. These effector mechanisms characterize the dynamical properties of the block labelled ANS in Figure 4.

a linear, time-invariant impulse response which maps fluctuations in instantaneous lung volume ($Q_{lu}(t)$; see Section 2.3) to fluctuations in $F(t)$. The impulse response is defined here by a linear combination of $s(t)$ and $p(t)$, each of which are advanced in time by 1.5 s in order to account for the noncausality of this mechanism [6, 9].

2.3 Resting Physiologic Perturbations

Respiratory activity, which may either be at fixed-rate or random-intervals [1], is modeled in terms of $Q_{lu}(t)$. Fixed-rate $Q_{lu}(t)$ is represented by a pure sinusoid, which is characterized by tidal volume (Q_t) and respiratory period (T_r), as well as a DC offset representing the functional reserve volume of the lungs (Q_{fr}). Each respiratory cycle of random-interval $Q_{lu}(t)$ is also represented by one period of a sinusoid with the DC offset Q_{fr}. However, the period is not constant here but rather determined based on the outcome of a probability experiment (which ranges from one to 15 seconds with a mean of five seconds), and the tidal volume is set such that the instantaneous alveolar ventilation rate (which considers the dead space in the airways (Q_{ds})) is identical to that of fixed-rate breathing.

In order to account for the mechanical effects of $Q_{lu}(t)$ on $P_{th}(t)$ and $P_{alv}(t)$, the simple model of ventilation, illustrated in Figure 6 in terms of its electrical circuit analog, is also incorporated in the model. The electrical components may be interpreted similarly to those in Figure 1 by considering air here rather than blood. Hence, the resistor (R_{air}) may be thought of as a conduit for airflow between the atmosphere and the lungs, while the capacitor may be interpreted as an air volume container representing the lung compartment, which is parametrized by an unstressed

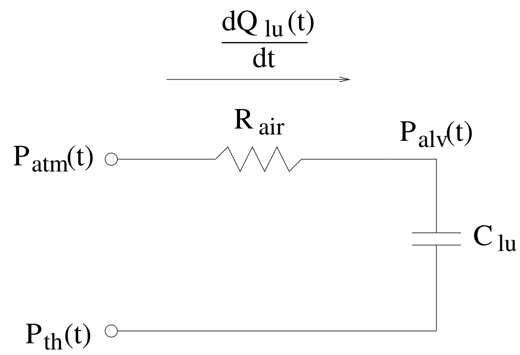


Figure 6: Electrical circuit analog of the human ventilatory mechanics model.

volume (Q_{lu}^0) in addition to C_{lu}.

The systemic effects of the autoregulation of local vascular beds is represented with an exogenous disturbance to $R_a(t)$ which is defined by a bandlimited Gaussian white noise process. This process is created by convolving Gaussian white noise of zero mean and *stdwr* standard deviation with a lowpass filter (truncated unit-area sinc function) of desired frequency cutoff (*fco*). Higher brain center activity impinging on the ANS is modeled with a *1/f* exogenous, Gaussian disturbance to $F(t)$ convolved with a filter defined by a linear combination of $s(t)$ (β-sympathetic sublimb) and $p(t)$. The *1/f* Gaussian disturbance is created by convolving Gaussian white noise of zero mean and *stdwf* standard deviation with a unit-area filter of *1/f*^{alpha} magnitude squared frequency response from 10^{-4} Hz to 1 Hz, where *alpha* is set to one. Each of these exogenous disturbances are treated as unobservable quantities.

3 Source Code

The *RCVSIM* source code was written predominantly in the MATLAB language (version 5.3.1; R11.1) and includes some C language necessary for on-line viewing and parameter updating. The source code may be compiled using the MATLAB compiler (version 1.2) with the libc5 development environment at the MATLAB prompt (see Section 4.2). Note that compilation permits software execution at the Linux prompt *and* greatly improves execution speed. The source code not only consists of code to implement the models described in Section 2 but also includes code to implement other models. These latter models have been minimally tested and documented and may only be executed in the MATLAB environment. A description of the code for implementing the models of Section 2 and an explanation of how this code may be modified or extended to implement arbitrary lumped parameter cardiovascular models are provided below. See Appendix A for a brief description of the other models and the source code for executing them.

3.1 Flowchart and Functions

The source code is based on the MATLAB function *simulate.m*. The input arguments to *simulate.m* include the desired parameter values characterizing the human cardiovascular model and its execution, while the outputs are the simulated data – all pressures ($P(t)$), volumes ($Q(t)$), flow rates ($\dot{q}(t)$), ventricular elastances $E(t)$, adjustable parameters ($ap(t)$), cardiac function/venous return curves ($numerics$), and ventricular contraction times (qrs). This function may also write the simulated data to file (with a desired prefix file name also provided as an input argument) and display the data as they are being calculated. The function is responsible for executing the models described in Section 2 as well as in Appendix A. However, the flowchart of Figure 7 depicts how the function simulates the data from the desired parameter values characterizing only the models of Section 2. The pertinent details of each block of the flowchart are provided below.

- *Declaring and Initializing Variables (t=0).* With the desired parameter values provided as function input arguments, all variables of the simulation are declared and initialized. Memory is pre-allocated for all of the data to be simulated over their entire integration period in order to increase execution speed with the MATLAB compiler. The respiratory-related waveforms are pre-computed over the entire integration period.

- *Numerical Integration for Calculating $P(t)$.* The pressures of the desired model of the pulsatile heart and circulation are calculated at the current time step ($t + T_s$) from the pressures at the previous time step (t) by fourth-order Runge-Kutta integration of the set of ordinary differential equations governing the model. T_s must be set to $\sim$0.005 s for reasonable accuracy.

- *Adjusting Parameters by Regulation/Perturbations.* Parameters of the pulsatile heart and circulation are adjusted by the short-term regulatory system and resting physiologic perturbations models. Because of the relatively narrow bandwidths of these models, the parameter adjustments are calculated at a sampling period of 0.0625 s. First, the requisite waveforms originally computed at a sampling period of T_s are decimated to a sampling period of 0.0625 s by averaging over the past 0.25 s every 0.0625 s. Then, the mandated parameter adjustments are computed at a sampling period of 0.0625 s. Finally, the mandated parameter adjustments are converted to a sampling period of T_s via linear interpolation (with the exception of the adjustments to $C_{l,r}^{es}$ which do not take effect until the initiation of the next ventricular contraction) in order to compute the subsequent waveforms.

- *Establishing qrs via "Integrate and Fire."* The mandated changes to $F(t)$ are mapped to the times of onset of ventricular contraction by integrating $F(t)$ (in units of bps) over time until the integral is equal to one. Then, systole is initiated by resetting the variable, ventricular elastance model, the integral is set to zero, and the integration is repeated.

- *Heart-Lung Unit or Systemic Circulation? $\xrightarrow{yes}$ Varying P_v, P_a, C_r^{ed} and Averaging $P_{\text{``}ra\text{''}}(t)$, $\dot{q}_v(t)$.* Cardiac function or venous return curves are generated, if desired. Following every fifth beat, $P_v$ and $P_a$ are varied in steps for generation of cardiac function curves, and $C_r^{ed}$ is varied for simulation of venous return curves. Time-averaged $P_{\text{``}ra\text{''}}(t)$ and $\dot{q}_v(t)$ and P_a (for cardiac function curves) are recorded over the beat preceding the step variation.

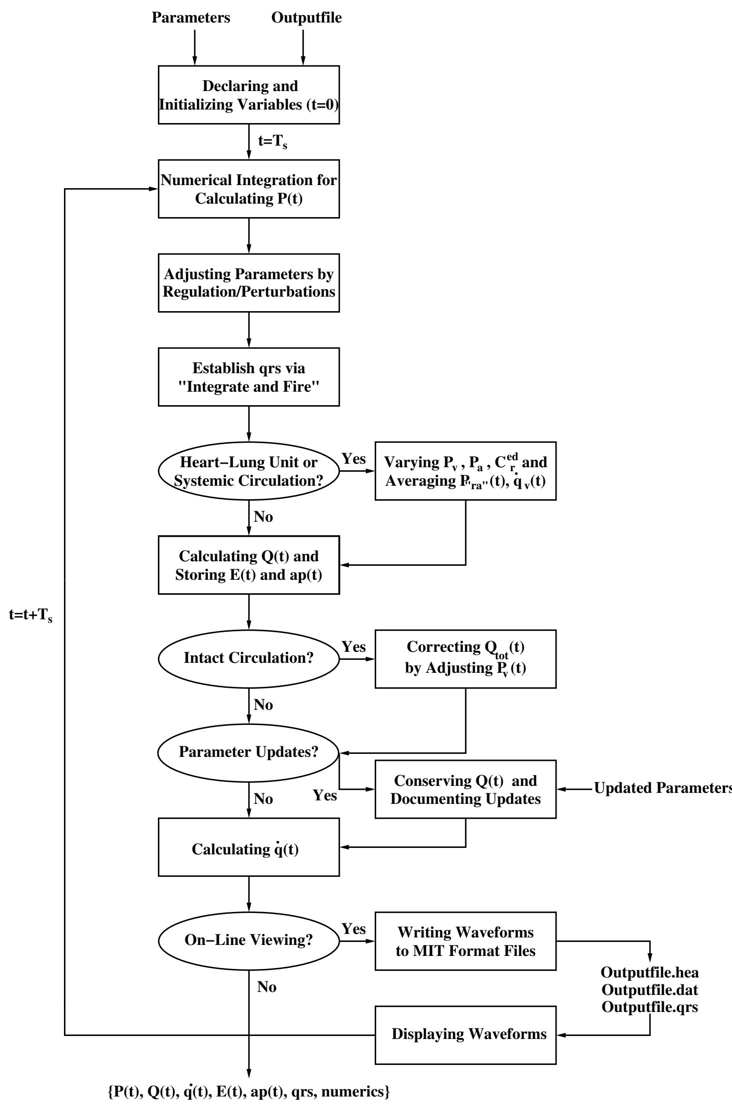


Figure 7: Flowchart of the MATLAB function *simulate.m*.

- *Calculating $Q(t)$ and Storing $E(t)$ and $ap(t)$.* The blood volumes of each compartment of the desired model of the pulsatile heart and circulation are computed at the current time step from the pressures at the current time step, and the values of the ventricular elastances and adjustable parameters at the current time step are stored into their pre-allocated memory slots.

- *Intact Circulation? $\xrightarrow{yes}$ Correcting $Q_{tot}(t)$ by Adjusting $P_v(t)$.* Total blood volume of the intact pulsatile heart and circulation at the current time step ($Q_{tot}(t)$), which may vary due to integration error, is conserved. The difference between the computed $Q_{tot}(t)$ and its assigned value is added/removed from $Q_v(t)$ and $P_v(t)$ is altered accordingly.

- *Parameter Updates? $\xrightarrow{yes}$ Conserving $Q(t)$ and Documenting Updates.* The parameter values of a simulation may be updated after the initiation of each ventricular contraction by pausing the simulation, updating the parameter values, and resuming the simulation. The newly chosen parameter values are documented to file if they are relevant to the current simulation, and the blood volumes in each compartment at the current time step are conserved by adjusting the pressures at the current time step (if necessary). Adjustments to the respiratory-related waveforms are implemented for the remainder of the integration period.

- *Calculating $\dot{q}(t)$.* The flow rates of the pulsatile heart and circulation models are calculated at the current time step from the pressures at the current time step.

- *On-Line Viewing? $\xrightarrow{yes}$ Writing Waveforms to MIT Format Files $\xrightarrow{yes}$ Displaying Waveforms.* When viewing simulated data as they are being calculated, the waveforms are periodically written to file in MIT format (with a desired period). The newly written data are then immediately displayed with WAVE.

The flow of each of the blocks is then repeated starting at *Numerical Integration for Calculating* $P(t)$ with $t = t + T_s$. In order to execute the blocks in the flowchart, *simulate.m* calls upon many MATLAB and C functions, each of which are briefly described below.

- *intact_init_cond.m* computes the initial pressures, volumes, and flow rates of the intact pulsatile heart and circulation model from the desired parameter values. The initial values are determined from the solution of a linear system of equations which are derived from the application of steady-state conservation laws to a linearized version of the model.

- *hlu_init_cond.m* computes the initial pressures, volumes, and flow rates of the heart-lung unit preparation model from the desired parameter values. The initial values are determined from the solution of a linear system of equations which are derived from the application of steady-state conservation laws to a linearized version of the model.

- *sc_init_cond.m* computes the initial pressures, volumes, and flow rates of the systemic circulation preparation model from the desired parameter values. The initial values are determined from the solution of a linear system of equations which are derived from the application of steady-state conservation laws to a linearized version of the model.

- *rk4.m* computes the pressures of the pulsatile heart and circulation (any preparation) at the current time step from the pressures of the previous time step, the current values of the parameters, respiratory-related waveforms, and time surpassed in the current cardiac cycle according to fourth-order Runge-Kutta integration.

- *intact_eval_deriv.m* is called only by *rk4.m* and computes the derivative of the intact pulsatile heart and circulation pressure values at a desired time step which is necessary for the fourth-order Runge-Kutta integration.

- *hlu_eval_deriv.m* is called only by *rk4.m* and computes the derivative of the heart-lung unit preparation pressure values at a desired time step which is necessary for the fourth-order Runge-Kutta integration.

- *sc_eval_deriv.m* is called only by *rk4.m* and computes the derivative of the systemic circulation preparation pressure values at a desired time step which is necessary for the fourth-order Runge-Kutta integration.

- *var_cap.m* is also called by *intact_eval_deriv.m, hlu_eval_deriv.m, and sc_eval_deriv.m* and computes a ventricular elastance value as well as its derivative at a desired time step from the current values of $C^{es}_{l,r}$, $C^{ed}_{l,r}$, the previous cardiac cycle length, and the time surpassed in the current cardiac cycle.

- *vent_vol.m* is also called by *intact_eval_deriv.m, hlu_eval_deriv.m, and sc_eval_deriv.m* and computes the current ventricular blood volume from the current ventricular pressure according to Newton's search method with an initial guess given by the previous ventricular blood volume.

- *rand_int_breath.m* computes the time until the next respiratory cycle commences based on the outcome of an independent probability experiment.

- *resp_act.m* computes the respiratory-related waveforms ($Q_{lu}(t)$, $P_{th}(t)$, $\frac{dP_{th}(t)}{dt}$, and $P_{alv}(t)$) over the entire integration period from the parameter values and the times of commencement of each respiratory cycle.

- *ilv_dec.m* decimates $Q_{lu}(t)$ to a sampling period equal to 0.0625 s. This decimated waveform is convolved with the filter created by *dncm_filt.m* (see below) in order to establish the changes in $F(t)$ mandated by the direct neural coupling mechanism.

- *dncm_filt.m* generates a filter which characterizes the direct neural coupling mechanism between $Q_{lu}(t)$ and $F(t)$.

- *bl_filt.m* generates a lowpass filter with a narrow transition band (truncated sinc function of unit-area) and desired cutoff frequency which is utilized to bandlimit the exogenous disturbance to R_a.

- *oneoverf_filt.m* generates a filter with a *1/f*^{alpha} magnitude-squared frequency response over a desired frequency range (in decades) and at a desired sampling period (see below).

- *ans_filt.m* creates a filter which is a linear combination of $s(t)$ and $p(t)$. This filter is convolved with the filter generated by *oneoverf_filt.m* and then white noise in order to create the exogenous disturbance to $F(t)$.

- *abreflex.m* computes the parameter adjustments mandated by the arterial baroreflex system based on the current setpoint and static gain values.

- *cpreflex.m* computes the parameter adjustments mandated by the cardiopulmonary baroreflex system based on the current setpoint and static gain values.

- *param_change.m* determines whether the parameter updates are relevant to the status of the current simulation based on the current parameter values, the previous parameter values, and the status parameters (see Section 5.2).

- *conserve_vol.m* computes the pressures at the current time step necessary to conserve the blood volume in each compartment at the current time step when parameter values are updated.

- *read_param.m* reads a file which contains the parameters values of the cardiovascular model and its execution in a specific format and stores the values in a MATLAB vector.

- *read_key.c* reads the standard input, pauses the simulation if a "p" is entered followed by <RETURN>, and resumes the simulation if a "r" is entered followed by <RETURN>.

- *write_param.c* copies the parameter file to a new file of the same name but with the extension *.num*. This function is implemented when the parameter update occurs. The extension is set equal to the number of parameter updates that have been made during the simulation period.

- *wave_remote.c* plots the desired simulated waveforms and annotations with the WAVE display system. This function is called when the simulated data are written to file in MIT format and plots the most recent desired window of written data.

The function *simulate.m* is called by a wrapper function *rcvsim.m* for execution at the Linux prompt. This wrapper function takes two command line arguments: 1) the name of a file containing the desired parameter values and 2) the prefix name of the output files to be generated in MIT format. The function *rcvsim.m*, which also includes a help option, reads in the parameter file with *read_param.m* (see above), creates a header file in MIT format, executes *simulate.m*, writes the simulated data to MIT format files if the on-line viewing option is not chosen, and displays cardiac function and venous return curves, if desired, with the function *plot_cfvr.c* (which employs Gnuplot). In order to execute *rcvsim.m*, the function must be compiled with the file *make.m* which creates the binary file *rcvsim*. The function *simulate.m* may also be compiled independently of *rcvsim.m* with the file *makem.m* which creates the binary file *simulate.mexlx* (in the Linux environment). Each of these make files greatly improve execution speed specifically through *mcc* (MATLAB compiler) optimization arguments *r* (real numbers only) and *i* (no dynamic memory allocation). Note that *simulate.m* may only be executed in the MATLAB environment without on-line viewing and parameter updating capabilities.

3.2 Modifications and Extensions

Although the human cardiovascular model upon which *RCVSIM* is based accounts for a wide variety of hemodynamic behaviors, it certainly cannot address arbitrary cardiovascular research objectives. For example, if the researcher is interested in analyzing how stroke volume is compromised at very high heart rates ($> \sim 150$ bpm) in the absence of cardiovascular regulation, the model, as described in Section 2, would not be adequate because contracting atrial compartments are not explicitly included. In such cases, the researcher may utilize the *RCVSIM* source code as a basis for facilitating the construction of a model which can address his research objective. An outline of the major steps necessary for the researcher to create different lumped parameter pulsatile heart and circulation models and add new bandlimited regulatory systems (*e.g.*, arterial chemoreflex) and resting physiologic perturbations (*e.g.*, central oscillator) is provided below. Note that additional steps may also be necessary depending upon the particular extension.

- Creating lumped parameter models of the pulsatile heart and circulation.

  1. Name the new lumped parameter model (*preparation*) and assign a unique number to it. This number will be used in conditional statements which must be added to the code in order to distinguish the desired preparation to be executed from the other possible preparations (see, for example, the *rk4.m* source code).
  2. Extend the MATLAB parameter vector (*th*) to include any additional, necessary parameters. Add the new parameters (in the correct format) to the parameter file (see Section 5.2). Expand the function *read_param.m* so that it can read these new parameters. If the researcher would like to implement the new preparation in the MATLAB environment, the function *header_def.m* must also be altered accordingly (see Appendix A).
  3. Create a function called *preparation_init_cond.m* to generate the initial pressures, volumes, and flow rates. Call this newly created function at the same point in *simulate.m* as the function call for *intact_init_cond.m*.
  4. Create a function called *preparation_eval_deriv.m* to calculate the derivative of the pressure values at a desired time step. Call this newly created function from *rk4.m* analogous to the function calls for *intact_eval_deriv.m*.
  5. Add code for calculating volumes and flow rates at the point in *simulate.m* in which these waveforms are computed for the other preparations.
  6. If necessary, pre-allocate additional memory for the simulated data in *simulate.m*, expand matrices to be written in MIT format in *simulate.m* and *rcvsim.m*, and extend code for generating the MIT format header file in *rcvsim.m*.
  7. Adjust parameter update code in *simulate.m* including *conserve_vol.m*.
  8. Add *preparation_init_cond.m* and *preparation_init_cond.m* to the make files (*make.m* and *makem.m*) and recompile the code.

- Adding *bandlimited* regulatory system/resting physiologic perturbation.

1. Name the new regulatory system/resting physiologic perturbation. This name will serve as a flag indicating whether the new addition is to be activated or not. The MATLAB vector *flag* at the start of *simulate.m* should be extended to incorporate this name.
2. Extend the MATLAB parameter vector (*th*) to include any additional, necessary parameters. Add the new parameters as well as the new flag name (in the correct format) to the parameter file (see Section 5.2). Expand the function *read_param.m* so that it can read these new parameters and flag name. If the researcher would like to implement the new model in the MATLAB environment, the function *header_def.m* must also be altered accordingly (see Appendix A).
3. Initialize the necessary variables at the beginning of *simulate.m*.
4. Create a function to compute the mandated change to the adjustable parameter. Call this function every 0.0625 s. If this function requires a simulated waveform as input, then this waveform must be averaged over the previous 0.25 s every 0.0625 s prior to the function call.
5. If a parameter other than $F(t)$, $R_a(t)$, $Q_v^0(t)$, and $C_{l,r}^{es}(t)$ is adjusted, then the following steps must be undertaken:
   (a) Pre-allocate additional memory for the adjustable parameter matrix *ap* in *simulate.m*.
   (b) Expand the *thc* vector in *simulate.m* to include the new parameter to be adjusted.
   (c) Linearly interpolate the newly adjustable parameter.
   (d) Assign the mandated adjustment to the *ap* matrix in *simulate.m*.
   (e) Expand the *ap* matrix to be written in MIT format in *simulate.m* and *rcvsim.m*.
   (f) Adjust the parameter update code in *simulate.m* accordingly.
   (g) Extend code for generating the MIT format header file in *rcvsim.m* to include the newly adjustable parameter.
6. Add the new function to the make files (*make.m* and *makem.m*) and recompile the code.

4 Software Installation and Compilation

The researcher may download the *RCVSIM* software from PhysioNet and install and execute the pre-compiled binaries provided that he is running Linux. If the researcher also has access to MATLAB and its compiler (version 1.2), then he may modify and extend the source code as he wishes and then recompile it to create new binaries. Alternatively, if the researcher is running any other platform in which the WAVE display system is fully supported (*e.g.*, Solaris, SunOS) and has access to the MATLAB compiler (version 1.2), he may compile the source code and install and execute the new binaries on that platform. (The binaries created for such platforms may then be uploaded to PhysioNet so that they may be distributed to other researchers who do not own MATLAB.) Detailed instructions on installing the *RCVSIM* binaries (and required libraries) and compiling the source code are provided below.

4.1 Installation

The installation steps that the researcher must carry out in order to execute the *RCVSIM* pre-compiled Linux binaries are as follows:

1. Download the file *rcvsim.tar.gz* from the following web page:
   http://www.physionet.org/physiotools/rcvsim

2. Type the following commands at the Linux prompt:
   tar xvzf rcvsim.tar.gz
   cd rcvsim

   The contents of this directory – henceforth referred to as *$DIR* – are as follows:

   - *README.* This text file includes a brief introduction, references to the *INSTALL* file and the *doc* sub-directory, and basic execution and compilation instructions.

   - *INSTALL.* This text file explains how to install/uninstall the *RCVSIM* software on Linux or other platforms in which the WAVE display system is fully supported.

   - *install.* This shell, executable script automates some, or all, of the installation process.

   - *uninstall.* This shell, executable script is designed to undo what was done by the *install* script.

   - *src.* This sub-directory includes all the source code described in Section 3.1 and Appendix A as well as two other C files (*check_redhat.c* and *check_wfdb.c*) which are required by the *install* and *uninstall* shell scripts. The Linux and MATLAB pre-compiled binaries (*rcvsim* and *simulate.mexlx*) are also stored here.

   - *bin.* This sub-directory includes parameter files, *parameters.def* and *header_def.m* (see Section 5.2 and Appendix A), which are respectively required for execution at the Linux and MATLAB prompts, a *wfdbcal* file responsible for scaling the simulated waveforms displayed by WAVE, and the two binaries, *check_redhat* and *check_wfdb*.

   - *lib.* This sub-directory consists of libraries which are required for executing the binaries. These libraries include the dynamic MATLAB libraries which permit software execution in the absence of MATLAB, two RPMs containing libc5 libraries and an old ld.so dynamic linker (part of the Redhat 6.2 distribution which are necessary for dynamically linking the MATLAB libraries), and a tar file consisting of the WFDB software package (version 10.1.6).

   - *doc.* This sub-directory includes this very document in HTML, PDF (*manual.pdf*), PostScript (*manual.ps*) and LaTeX source (*manual.tex*) formats.

3. Login as root.

4. Download and install the WFDB software package and the WAVE display system, if this has not already been done. See the following web page for instructions:
   http://www.physionet.org/physiotools/wfdb-linux-quick-start.shtml

If the researcher is running Linux Redhat 6.2 or higher, then

5. Type the following command in the *$DIR* directory:
   ./install

The results of Step 5. are as follows:

- The WFDB Software Package (version 10.1.6) in the *$DIR/lib* directory will be installed, if an older version is currently installed.
- The libc5 libraries and old ld.so dynamic linker RPMs in the *$DIR/lib* directory will also be installed. (Note that recent Linux systems use libc and a new linker but will not be affected by the installation of the older libraries and linker.)
- An *rcvsim* executable shell script will be placed in the *$DIR/bin* directory. This script sets the library and WFDB paths for its subsequent execution of the binary *$DIR/src/rcvsim* and is linked to the directory */usr/local/bin* which should already be in the researcher's path.
- The MATLAB binary executable *simulate.mexlx* will be linked to a directory in the MATLAB path, if MATLAB is present.

Or, if the researcher is running Linux Redhat 6.1 or lower or any other Linux distribution (*e.g.*, Suse, Debian), then

5a. Acquire and install the necessary libc5 libraries and old dynamic linker, if they are not currently present on the system.

5b. Type the following command in the *$DIR* directory:
   ./install

For RPM-based distributions (*e.g.*, Mandrake), the software required for Step 5a. may be found on *rpmfind.net* as was the case for the RPMs provided in the directory *$DIR/lib*. Please see the following web pages:
http://www.rpmfind.net/linux/rpm2html/search.php?query=ld.so
http://www.rpmfind.net/linux/rpm2html/search.php?query=libc
Note that the results of Step 5b. differ from those of Step 5. in that the RPMs of *$DIR/lib* will *not* be installed.

6. To undo the *install* script, type the following command in the *$DIR* directory:
   ./uninstall

This will undo everything done by *install* except the removal of the WFDB Software Package (version 10.1.6), if it were installed. This software can be removed manually (read INSTALL file in the tar file *wfdb-10.1.6.tar.gz* which is located in the $DIR/lib directory).

4.2 Compilation

If the researcher is running Linux and wishes to modify/extend the *RCVSIM* source code or if the researcher would like to run the *RCVSIM* software on another platform in which WAVE is fully supported, then compilation is necessary. The steps required to compile the source code are are as follows:

1. Acquire and install MATLAB with the MATLAB compiler (version 1.2), if they are not currently available.

2. Establish a libc5 development environment. See the following web page for detailed instructions:
http://www.mathworks.com/support/solutions/data/11129.shtml

3. Launch MATLAB from the *$DIR* directory.

4. At the MATLAB prompt, execute the following commands:
cd src
make
makem

By implementing these steps in the Linux environment, new *rcvsim* and *simulate.mexlx* binaries will be created in the *$DIR/src* directory. If the *RCVSIM* software has already been installed, then re-installation is unnecessary after compilation. On platforms other than Linux, the above steps must be carried out prior to software installation on platforms other than Linux. Additionally, the *install* and *uninstall* scripts in the *$DIR* directory need to be slightly modified in order to include the different MATLAB binary file extension name that results from compiling on a different platform. For example, if compilation is achieved on the Solaris platform, *simulate.mexlx* in the *install* and *uninstall* files must be replace with *simulate.mexsol* as the latter file will be created in the *$DIR/src* directory. Then, the newly compiled software may be installed according to the previous section.

Note that it is possible to compile the source code with the latest MATLAB compiler (version 2.1). However, the binaries generated from this compiler are on the order of three magnitudes *slower* than those generated with the MATLAB compiler (version 1.2). Mathworks is currently trying to improve the latest compiler, so it may be possible in the future to use this compiler.

5 Software Execution

The researcher may view and record data simulated from the human cardiovascular model of Section 2 by running the *rcvsim* executable file at the Linux prompt. Detailed instructions explaining how to execute this file including several examples, are provided below. Execution of *simulate.mexlx* at the MATLAB prompt is touched upon in Appendix A. (Note that this section requires some familiarity with the WAVE display system which may be acquired by either typing *more /usr/help/wave/wave.hlp* at the Linux prompt or visiting the web page:
http://www.physionet.org/physiotools/wug/.)

5.1 Help Option

A help option may be implemented by running the *rcvsim* executable with the single argument *-h* at the Linux prompt (that is, *rcvsim -h*; see Figure 8). The help option provides a description of the major components of the human cardiovascular model, command line arguments, generated output files, and on-line viewing options.

According to the help option, the executable file requires two arguments at the command line in order to simulate hemodynamic data. The first argument must be the name of a file in the current directory which contains the desired parameter values characterizing the human cardiovascular model and its execution. This is the working parameter file which may be updated during the simulation period (see Section 5.2). The second argument must be the desired prefix name of the output files to be generated by the model.

By executing *rcvsim* with these two arguments, three MIT format files are always generated in the current directory with extensions *.dat*, *.qrs*, and *.hea*. The *.dat* file is a binary (shorts) file consisting of all of the generated waveforms; the *.qrs* file is a binary file consisting of annotations which include the times of onset of ventricular contractions as well as any parameter updates; and the *.hea* file is an ASCII header file necessary for reading, viewing, and analyzing the *.dat* and *.qrs* files with the open-source software provided by PhysioNet. A fourth file with the extension *.txt* may also be generated when the heart-lung unit preparation or systemic circulation preparation is implemented. This file is in ASCII, multi-column format and constitutes the simulated cardiac function or venous return curves. In order to document fully the simulation, the *rcvsim* executable also saves the working parameter file in the current directory each time it is updated. The name of the saved files is the first command line argument with the extension *.num* which denotes the number of parameter updates that have been made during the simulation period. The name of each saved file is also recorded in the annotation files at the time in which the parameters were updated. At the beginning of the simulation, the *rcvsim* executable saves the initial working parameter file with extension *.0* to the current directory.

The *rcvsim* executable also permits the simulated waveforms (as a function of time) to be viewed as they are being calculated (on-line viewing) through the WAVE display system. The simulation may be paused during on-line viewing by simply entering "p" followed by <RETURN> at the standard input. Once the simulation is paused, any and all of the following three actions may be carried out. 1) All the data that have been generated up to the time of the pause may be scrolled through with the arrow buttons at the top of the WAVE display system. 2) Plots of one generated waveform against another may be displayed by clicking the File button at the top of the WAVE display system (with the right mouse button), and then clicking on the Analyze... option followed by the VCG button (both with the left mouse button). The first two waveforms appearing in the Signal List (first waveform is plotted on x-axis and the second waveform, on y-axis), which may be adjusted as desired, will then be plotted against each other via Gnuplot. 3) The working parameter file may be updated *and saved*. The simulation may be resumed, with the updated parameter values, by simply entering "r" followed by <RETURN> at the standard input. Note that plots of one waveform versus another will not be automatically updated upon resuming the simulation. However, these plots may be manually updated by subsequently pausing the simulation and regenerating the plot as described above.

```
[rmukkama@cvsim src]$ rcvsim -h
The function rcvsim executes a computational model of the
cardiovascular system.  The model includes the following
components:
1) lumped parameter, pulsatile heart and circulation (intact,
   heart-lung unit, or systemic circulation)
2) short-term regulatory system
   a) arterial baroreflex system
   b) cardiopulmonary baroreflex system
   c) direct neural coupling mechanism between respiration
      and heart rate
3) resting physiologic perturbations
   a) respiration
   b) autoregulation of local vascular beds
      (bandlimited disturbance to systemic arterial resistance)
   c) 1/f disturbance to heart rate

Command line arguments:

rcvsim parameterfile outputfile

where

parameterfile - name of working file which contains the current parameter
                values characterizing the model (must be in current directory)
   outputfile - prefix of the output files generated by the model

or

rcvsim -h for help

Output files:

   outputfile.dat - binary file (MIT format -- shorts) containing all
                    generated waveforms
   outputfile.qrs - qrs annotations file (MIT format)
   outputfile.hea - header file (MIT format) describing the contents
                    of outputfile.dat
   outputfile.txt - ascii, multi-column file representing either
                    cardiac function or venous return curves
parameterfile.num - parameter file characterizing execution;
                    created after each parameter update beginning with
                    the initial choice of values (num = 0);
                    see aux information in outputfile.qrs for
                    for time in which this file is created

During on-line viewing,

Press p and RETURN at standard input to pause

Once paused, the following actions may be carried out:
1) scrolling backwards with arrow buttons
2) plotting waveforms against each other by clicking on File
   (with the right mouse), then, Analyze..., and then VCG
   (the first two waveforms in Signal List will be plotted
   against each other)
3) update parameters in parameterfile and save parameterfile

Press r and RETURN at standard input to resume
[rmukkama@cvsim src]$
```

Figure 8: Results of executing the *rcvsim* help option at the Linux prompt.

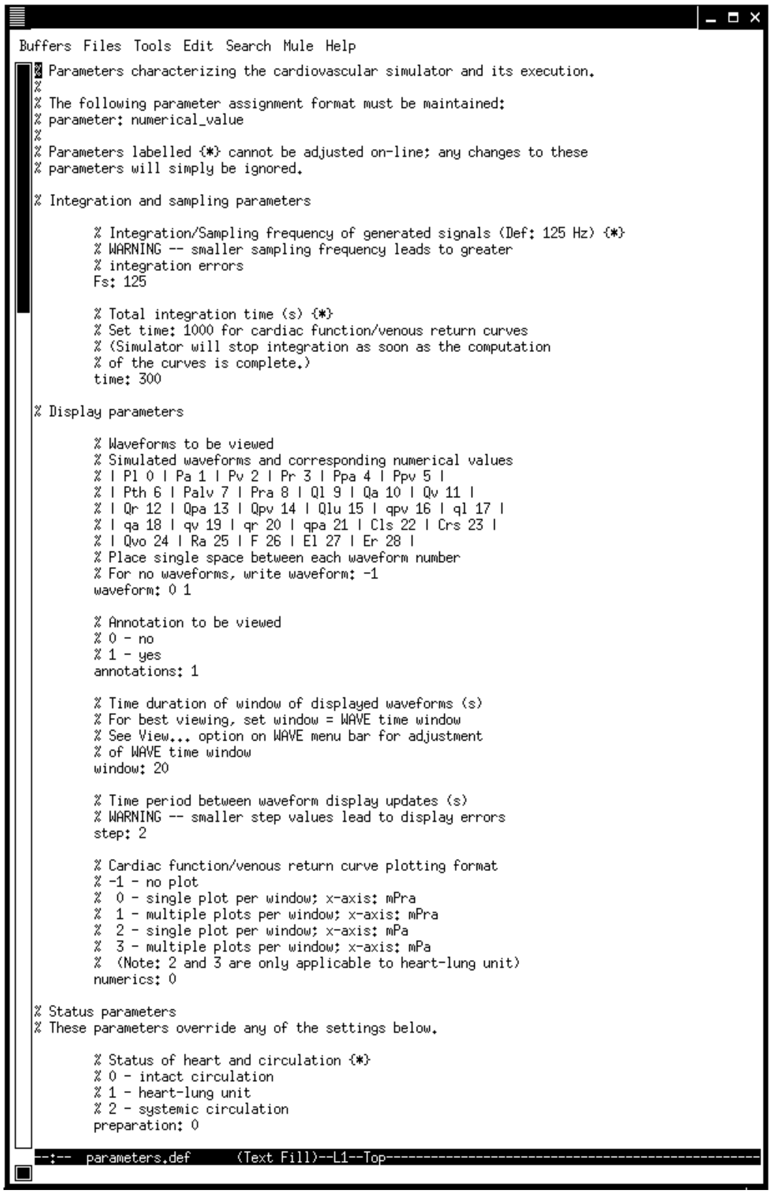
5.2 Parameter File

The parameter file (*$DIR/parameters.def*; see Figure 9) assigns the desired numerical values to all of the parameters characterizing the human cardiovascular model and its execution. The syntax for parameter assignment must be precisely as written *within* the following squiggly brackets: {*parameter: numerical_value*}. Otherwise, the parameters will not be read in properly. The parameter file also includes definitions of each of the parameters and default or nominal parameter values. Each line containing these definitions and default values as well as any other comments must be preceded by a %. Parameter assignments should never be preceded by a %, else they will not be read in properly. Each of the parameters in the file may be updated in the midst of a simulation period with the exception of those labelled with {*}. Any update to these parameters will simply be ignored.

The parameter file consists of integration and sampling parameters; display parameters; status parameters; pulsatile heart and circulation parameters; short-term regulatory system parameters, and resting physiologic perturbation parameters. The status parameters are flags which indicate the preparation of the pulsatile heart and circulation to be implemented as well as whether a particular short-term regulatory system or resting physiologic perturbation is to be activated or deactivated. The status parameters, which cannot be adjusted in the midst of a simulation period, override any of the other relevant parameters assignments. For example, if *dra* is set to zero, then the exogenous disturbance to R_a is deactivated and may not be activated during the simulation period regardless of the value assigned to *stdwr*, which establishes the standard deviation of the disturbance to R_a. Note that a short-term regulatory system or resting physiologic perturbation may also be deactivated through the parameters that characterize them. For example, the exogenous disturbance to R_a may be deactivated by setting *stdwr* to zero. In this case, the exogenous disturbance to R_a may be subsequently activated during the simulation period by setting *stdwr* to a value greater than zero. However, if the researcher knows that a short-term regulatory system or resting physiologic perturbation is not required for his simulation, then the appropriate status parameter should be deactivated for the purposes of increasing execution speed. Note that the pulsatile heart and circulation parameters may be applicable to the intact circulation, heart-lung unit, and/or systemic circulation preparations and are labelled accordingly.

5.3 Viewing Waveforms

Provided that the display parameters are properly set, the researcher may view the simulated waveforms and update the parameter values on-line by running the *rcvsim* executable which will make repeated function calls to the WAVE display system. Alternatively, the waveforms, which are recorded to MIT format files, may be viewed at any time after completion of the simulation (off-line viewing) by directly running the *wave* executable file at the Linux prompt. An explanation on how to set the display parameters and caveats to on-line parameter updating are provided below. See also Examples 1-7 in Section 5.5 which illustrate how to view waveforms both on-line and off-line.



```
Buffers Files Tools Edit Search Mule Help
% Parameters characterizing the cardiovascular simulator and its execution.
%
% The following parameter assignment format must be maintained:
% parameter: numerical_value
%
% Parameters labelled {*} cannot be adjusted on-line; any changes to these
% parameters will simply be ignored.

% Integration and sampling parameters

        % Integration/Sampling frequency of generated signals (Def: 125 Hz) {*}
        % WARNING -- smaller sampling frequency leads to greater
        % integration errors
        Fs: 125

        % Total integration time (s) {*}
        % Set time: 1000 for cardiac function/venous return curves
        % (Simulator will stop integration as soon as the computation
        % of the curves is complete.)
        time: 300

% Display parameters

        % Waveforms to be viewed
        % Simulated waveforms and corresponding numerical values
        % | Pl 0 | Pa 1 | Pv 2 | Pr 3 | Ppa 4 | Ppv 5 |
        % | Pth 6 | Palv 7 | Pra 8 | Ql 9 | Qa 10 | Qv 11 |
        % | Qr 12 | Qpa 13 | Qpv 14 | Qlu 15 | qpv 16 | ql 17 |
        % | qa 18 | qv 19 | qr 20 | qpa 21 | Cls 22 | Crs 23 |
        % | Qvo 24 | Ra 25 | F 26 | El 27 | Er 28 |
        % Place single space between each waveform number
        % For no waveforms, write waveform: -1
        waveform: 0 1

        % Annotation to be viewed
        % 0 - no
        % 1 - yes
        annotations: 1

        % Time duration of window of displayed waveforms (s)
        % For best viewing, set window = WAVE time window
        % See View... option on WAVE menu bar for adjustment
        % of WAVE time window
        window: 20

        % Time period between waveform display updates (s)
        % WARNING -- smaller step values lead to display errors
        step: 2

        % Cardiac function/venous return curve plotting format
        % -1 - no plot
        %  0 - single plot per window; x-axis: mPra
        %  1 - multiple plots per window; x-axis: mPra
        %  2 - single plot per window; x-axis: mPa
        %  3 - multiple plots per window; x-axis: mPa
        %  (Note: 2 and 3 are only applicable to heart-lung unit)
        numerics: 0

% Status parameters
% These parameters override any of the settings below.

        % Status of heart and circulation {*}
        % 0 - intact circulation
        % 1 - heart-lung unit
        % 2 - systemic circulation
        preparation: 0
--:--  parameters.def      (Text Fill)--L1--Top----------------------------
```

Figure 9: The *$DIR/parameters.def* file which contains the parameter values characterizing the human cardiovascular model of Section 2 and its execution.

5.3.1 Setting Display Parameters

The *waveform* parameter under the display parameters in the working parameter file determines whether the simulated waveforms are to be viewed on-line. If the *waveform* parameter is assigned the numerical value of -1, then the waveforms are not displayed as they are being calculated but may be subsequently viewed and analyzed off-line. The researcher may choose this option, if, for example, the data required for analysis are very time consuming to generate (*e.g.*, Monte Carlo simulations). If the *waveform* parameter is assigned one or more numerical values between 0 and 28 inclusive (with a single space inserted between each assigned numerical value), then the waveforms corresponding to those numerical values (see the *$DIR/pararmeters.def* file (Figure 9) or the generated file with extension *.hea* for mapping key between waveforms and numerical values) will be displayed as they are being calculated. For example, in Figure 9, the *waveform* parameter is set such that left ventricle and systemic arterial pressures will be displayed on-line. Note that the *annotations* parameter beneath the *waveform* parameter is simply a flag indicating whether the contents of the annotations file, which include the times of onset of ventricular contractions and parameter updates, will be viewed on-line with the waveforms selected by the *waveform* parameter. Note that if the *waveform* parameter is set to the numerical value of -1, then the contents of the annotations file will *not* be displayed on-line regardless of the value assigned to the *annotations* parameter.

The *rcvsim* executable file implements on-line viewing by periodically updating the WAVE display with the most recently computed window of waveforms. The time duration of the window and the update time period (both simulation times) may be respectively set to desired values with the *window* and *step* parameters. For optimal on-line viewing, the *window* parameter should be set equal to the time duration displayed by WAVE. This latter time duration is set by the physical size of the WAVE window as well as the Time scale variable which is essentially a calibration factor mapping this physical size to time duration. The Time scale variable may be altered by clicking the VIEW option on the WAVE menu bar. The *step* parameter should be chosen to be sufficiently small such that the displayed waveforms appear to scroll continuously through the WAVE window. However, if the *step* parameter is chosen to be too small, then the actual time required to update the display of the simulated data may not be sufficient and the quality of viewing may thus be compromised.

5.3.2 On-line Parameter Updating

All of the parameter assignments in the working parameter file may be updated as waveforms are being calculated and displayed on-line except those labelled with $\{*\}$. Any updates to these parameters will be ignored. As soon as any parameter (not labelled with $\{*\}$) is updated in the working parameter file, the file is saved (with a new name) in order to document fully the simulation (see Section 5.1). Some caveats to on-line parameter updating are provided below.

Since none of the display parameters are labelled with a $\{*\}$, they *are permitted* to be updated on-line. Thus, the researcher may, for example, change the waveforms that he is currently viewing without having to rerun *rcvsim*. However, when the working parameter file is updated *only* through the display parameters, the update will not be documented to file.

Updates to the working parameter file are also not documented when the particular update is not relevant to the status of the current simulation. For example, an update to the *Cls* parameter is relevant when the intact circulation and heart-lung unit preparations are being implemented. Thus, in this case, the update will be documented to file. However, when the systemic circulation preparation is being executed, an update to the *Cls* parameter is irrelevant (see Figure 3) and is thus not documented to file.

When implementing the heart-lung unit, the *Pv* and *Pa* parameters may be updated on-line provided that they are not being adjusted through the *Pvs* and *Pas* parameters, respectively. Otherwise, the on-line adjustment of the *Pv* and *Pa* parameters will be ignored. Similarly, when implementing the systemic circulation preparation, any update to the *Crd* parameter will be ignored unless it is not being adjusted through the *Crds* parameter.

As described in Section 3.1, the volume in each of the capacitive elements of the pulsatile heart and circulation (any preparation) is always conserved through a pressure adjustment. The only exception to this rule is naturally when the researcher desires to adjust total blood volume through the *Qtot* parameter (which is only applicable to the intact pulsatile heart and circulation preparation). In this case, the volume is added to or subtracted from the systemic venous volume and the systemic venous pressure is adjusted accordingly.

The instantaneous lung volume waveform may only be altered by updating the following parameters: *Tr*, *Qt*, *Qfrs*, and *Qds*. If parameters of the ventilatory model in Figure 6 are updated (which includes the *Pvc* parameter), the value of intrathoracic pressure at the functional reserve volume of the lungs will be adjusted instantaneously in order to preclude any change to instantaneous lung volume.

Finally, when updating the adjustable parameters of the pulsatile heart and circulation through the *F*, *Ra*, *Qvo*, *Crs*, and *Cls* parameters, the current values *and* the setpoint values of these parameters will be adjusted. Note that updates to the *Crs* and *Cls* parameters will take effect at the start of the subsequent ventricular contraction.

5.4 Viewing Cardiac Function and Venous Return Curves

Provided that the relevant parameters are properly set, the researcher may view cardiac function and venous return curves immediately after they have been calculated (on-line viewing) by running the *rcvsim* executable which will make a function call to Gnuplot. Since the time required for generating a cardiac function or venous return curve is relatively short (within a few seconds), the on-line viewing capability will usually suffice. However, it is possible that the researcher may also desire to view the curves off-line. Since the curves are written to file in ASCII, multi-column format, the researcher may view them any time after completion of the simulation by directly executing *gnuplot* at the Linux prompt. A description of how to set the relevant parameters is given below. See also Examples 8-13 in Section 5.5 which illustrate how to view the cardiac function and venous return curves both on-line and off-line. (Note that this section requires some familiarity with Gnuplot which may be garnered by typing *man gnuplot* at the Linux prompt.)

In order for the *rcvsim* executable to generate a cardiac function or venous return curve, either the heart-lung unit preparation or systemic circulation preparation must be implemented by assigning the *preparation* parameter under the status parameters a numerical value of 1 or 2. Provided that this has been done, then the *numerics* parameter under the display parameters determines whether the cardiac function/venous return curve is to be viewed on-line. If the *numerics* parameter is assigned the numerical value of -1, then the curve will not be displayed as soon as it is calculated but may be subsequently viewed off-line. If the *numerics* parameter is set to a numerical value between 0 and 3 inclusive which correspond to different plotting formats (see Figure 9), then the cardiac function/venous return curve will be automatically displayed immediately following the completion of the simulation. The different plotting formats can be best understood by recognizing that the on-line display of the curves is specifically implemented by writing gnuplot commands to a file in the */tmp* directory and executing these commands through a function call to *gnuplot*. The single plot per window formats (corresponding to numerical values of 0 and 2) will delete this file if it exists, write a new file to the */tmp* directory, and thus display only the cardiac function/venous return curve of the current simulation. The multiple plots per window formats (corresponding to numerical values of 1 and 3) will add plotting instructions to the existing file in the */tmp* directory and thus display the curve of the current simulation as well as all other curves that are instructed to be displayed in the file. In this way, multiple cardiac output and venous return curves can be overlayed on the same axes. The mPra x-axis formats (corresponding to numerical values of 0 and 1) will display either cardiac function or venous return curves. The mPa x-axis formats (corresponding to numerical values of 2 and 3) will display average cardiac output as a function of average systemic arterial pressure and is thus applicable only to the heart-lung unit preparation.

Whether cardiac function and venous return curves are to be viewed on-line or off-line, the simulation time is determined by the *time* parameter under integration and sampling parameters or the time it takes to complete the calculation of the entire curve, which ever is less. Hence, the *time* parameter should always be set to a value that is greater than the time it takes to calculate the entire curve (1000 seconds is usually more than enough).

In order to generate venous return curves, the *Crds* parameter under pulsatile heart and circulation parameters must be properly selected. This parameter determines the increments in which the *Crd* parameter is stepped from the value assigned to the *Crs* parameter to 60 ml/mmHg. Hence, this parameter determines the number of points to be calculated on the venous return curve. For example, if this parameter is set to five and all other parameters are also set to their default values, then 12 points on the venous return curve will be calculated. If the *Crds* parameter is set to a value greater than 60-*Crs*, then the *Crd* parameter will be held constant throughout the simulation and only one point on the venous return curve will be generated.

In order to generate cardiac function curves, the *Pvs* and *Pas* parameters under pulsatile heart and circulation parameters must be properly selected. Analogous to the *Crds* parameter, these parameters indicate the increments in which the *Pv* and *Pa* parameters are stepped. If the simulation of a cardiac output curve is desired, the *Pa* parameter should be held constant by setting the *Pas* parameter to a very large value (1000 mmHg will usually be more than sufficient), and the *Pvs* parameter should be set to a sufficiently small value in order to permit the generation of a reasonably smooth curve (2 mmHg will usually do). If the generation of a curve of average cardiac output versus average systemic arterial pressure is required, the *Pv* parameter should be held constant by setting the *Pvs* parameter to a very large value (100 mmHg will usually be more than sufficient), and the *Pas* parameter should be set to a sufficiently small value in order to allow the generation of a reasonably smooth curve (30 mmHg will usually do). Finally, note that the researcher may assign sufficiently small values to both *Pvs* and *Pas* such that a family of cardiac output curves at different systemic arterial pressures will be generated.

5.5 Viewing Examples

The following examples illustrate how to view waveforms and cardiac function/venous return curves on-line and off-line. Prior to implementing these examples, the researcher should set the time duration displayed by the WAVE window to 20 seconds by resizing the window and/or adjusting the Time scale variable (click VIEW option at the top of the WAVE menu bar).

Ex. 1

- *Desired Execution:*
  - On-line display of left ventricle pressure, volume, and flow rate.
  - Uncontrolled, unperturbed, intact pulsatile heart and circulation with default parameter values.
- *Required Steps:*
  1. Copy file *$DIR/bin/parameters.def* to the current directory with the new file name *parameters_1*.
  2. Open the file *parameters_1* with any text editor (*e.g.*, emacs).
  3. Re-assign the following parameters: *waveform: 0 9 17* and *annotations: 0*. Make sure all of the status parameters are set to zero.
  4. Save the file *parameters_1*.
  5. Run the following command at the Linux prompt:
     rcvsim parameters_1 foo1
- *Execution Output:*
  - The WAVE window in Figure 10 will initially appear and will automatically scroll through the simulated data as they are being generated. This process will terminate once 300 seconds of the data have been simulated.
  - The following files will be created in the current directory: *foo1.dat*, *foo1.qrs*, *foo1.hea*, and *parameters_1.0* which may subsequently be viewed off-line (See Example 2).

Ex. 2

- *Desired Execution:*
  - Off-line display of left ventricle pressure, volume, and flow rate.
  - Off-line display of left ventricle pressure versus volume.
  - Uncontrolled, unperturbed, intact pulsatile heart and circulation with default parameter values.
- *Required Steps:*

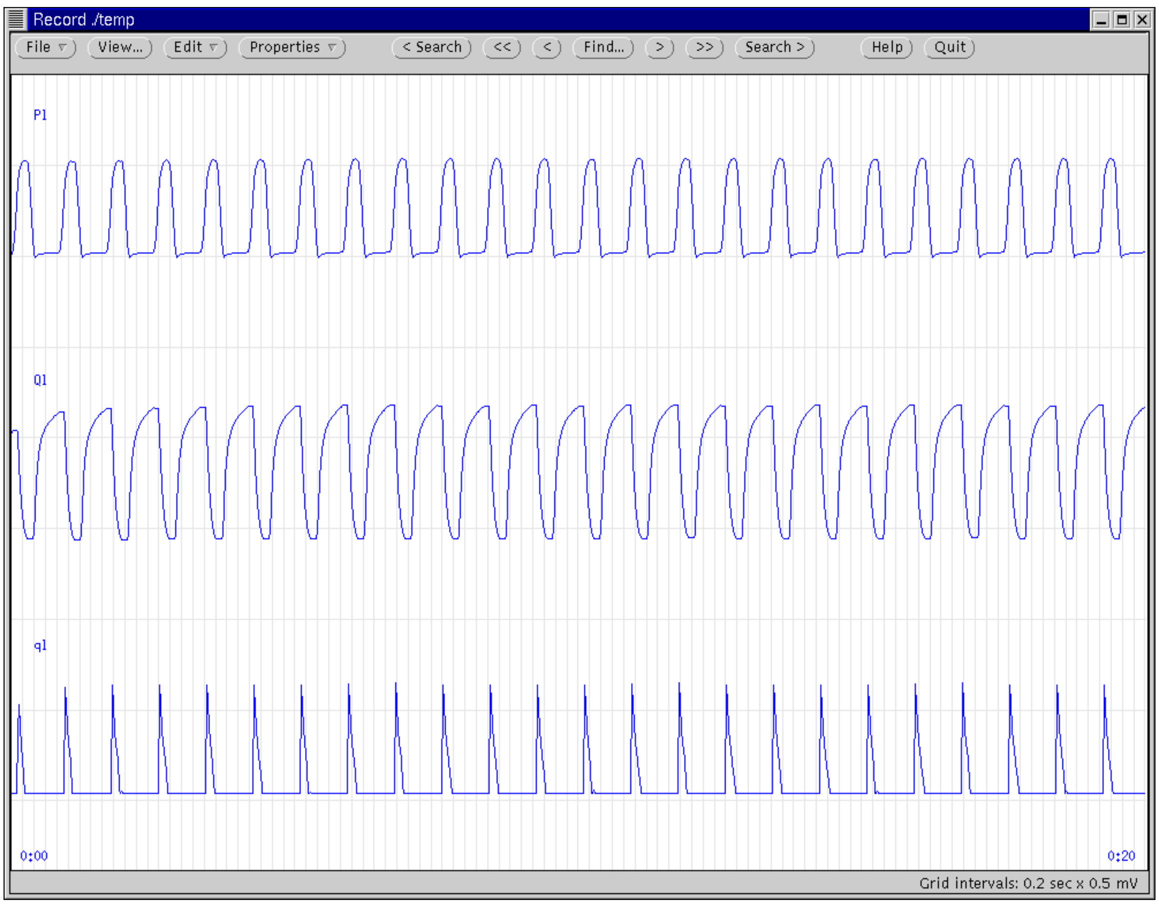


Figure 10: Initial WAVE window generated according to Ex. 1 and Ex. 2.

1. Copy file *$DIR/bin/parameters.def* to the current directory with the new file name *parameters_2*.
2. Open the file *parameters_2* with any text editor (*e.g.*, emacs).
3. Re-assign the following parameter: *waveform: -1*. Make sure all of the status parameters are assigned the numerical value of zero.
4. Save the file *parameters_2*.
5. Run the following command at the Linux prompt:
   rcvsim parameters_2 foo2.
6. Any time after the completion of the previous step, execute the following command at the Linux prompt:
   wave -r foo2 -s 0 9 17
7. Click on File button with right mouse button and then click Analyze... option with left mouse button. Change first two waveforms in the Signal List to 9 0 followed by <RETURN>. Then, click on the VCG button.

Or, if **Ex. 1** has been previously implemented, then

1. Execute the following command at the Linux prompt:
   wave -r foo1 -s 0 9 17
2. Click on File button with right mouse button and then click Analyze... option with left mouse button. Change first two waveforms in the Signal List to 9 0 followed by <RETURN>. Then, click on the VCG button.

- *Execution Output:*
  - If **Ex. 1** has not been previously implemented, then the following files will be created in the current directory: *foo2.dat*, *foo2.qrs*, *foo2.hea*, and *parameters_2.0*.
  - When the *wave* executable is implemented, the WAVE window in Figure 10 will again initially appear. The researcher may then use the arrow buttons at the top of the WAVE display system to scroll through the 300 seconds of generated waveforms.
  - When the VCG button is clicked, the Gnuplot in Figure 11 will appear illustrating left ventricle pressure-volume loops. (As described in Section 5.1, plotting one waveform against another can be carried out during on-line viewing provided that the simulation is paused. Moreover, any two generated waveforms may be plotted against each other through selection of the first two waveforms in the Signal List.)

Ex. 3

- *Desired Execution:*
  - On-line display of systemic arterial pressure, heart rate, and instantaneous lung volume with annotations.

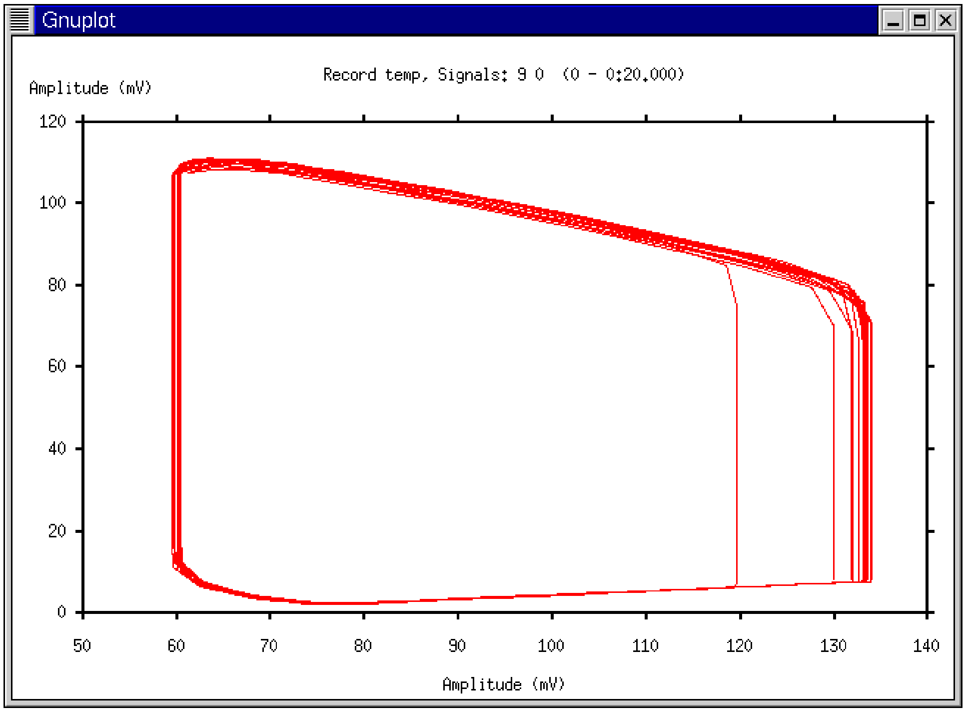


Figure 11: Gnuplot window generated according to Ex. 2.

- Fully controlled, fully perturbed (fixed-rate breathing), intact pulsatile heart and circulation with default parameter values.

- *Required Steps:*

  1. Copy file *$DIR/bin/parameters.def* to the current directory with the new file name *parameters_3*.
  2. Open the file *parameters_3* with any text editor (*e.g.*, emacs).
  3. Re-assign the following parameters: *waveform: 1 15 26*, *baro: 3*, *dncm: 1*, *breathing: 1*, *dra: 1*, and *df: 1*.
  4. Save the file *parameters_3*.
  5. Execute the following command at the Linux prompt:
     rcvsim parameters_3 foo3

- *Execution Output:*

  - A WAVE window will appear and will automatically scroll through the simulated data with annotations. Figure 12 illustrates the window after one minute of data has been calculated. This process will terminate once 300 seconds of data have been simulated.
  - The following files will be created in the current directory: *foo3.dat*, *foo3.qrs*, *foo3.hea*, and *parameters_3.0*.

Ex. 4

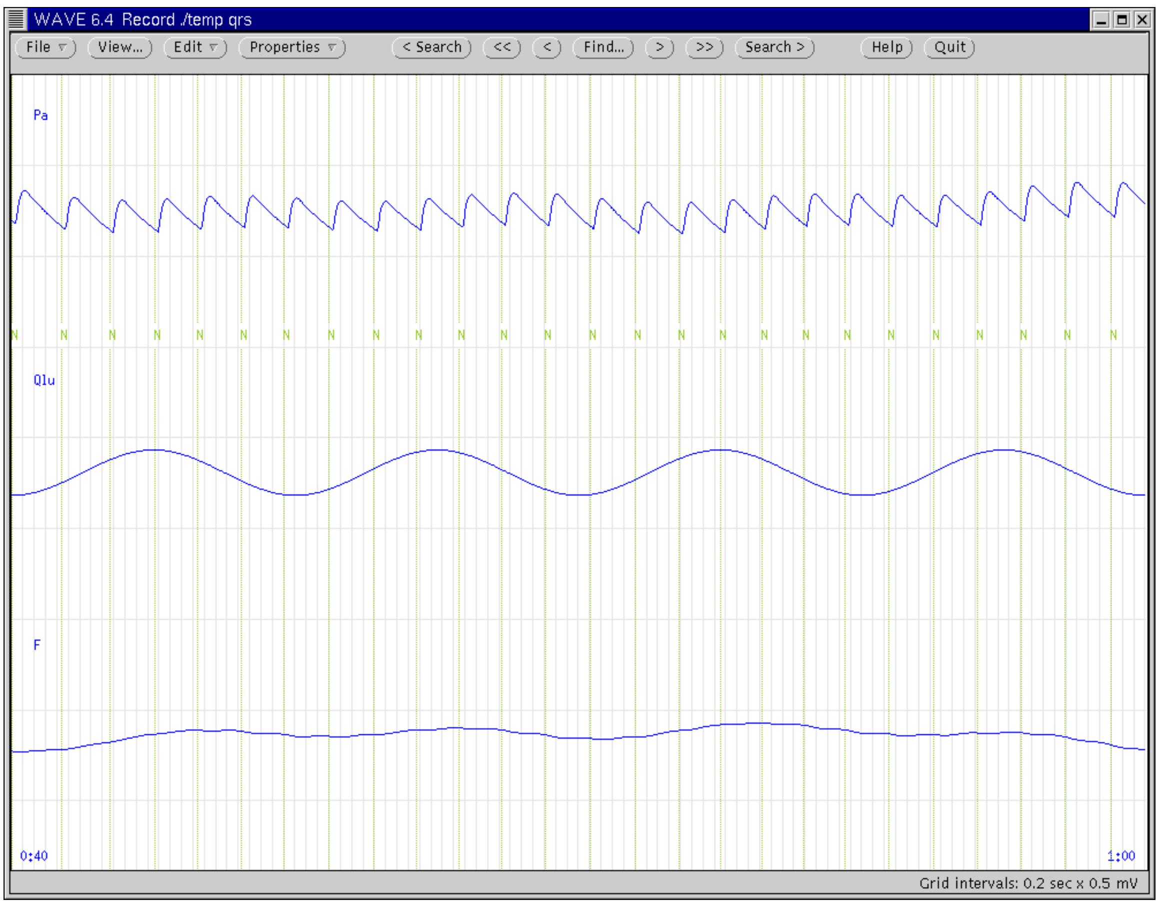


Figure 12: WAVE window generated according to Ex. 3 and Ex. 4.

- *Desired Execution:*
  - Off-line display of systemic arterial pressure, heart rate, and instantaneous lung volume with annotations.
  - Fully controlled, fully perturbed (fixed-rate breathing), intact pulsatile heart and circulation with default parameter values.
- *Required Steps:*
  1. Copy file *$DIR/bin/parameters.def* to the current directory with the new file name *parameters_4*.
  2. Open the file *parameters_4* with any text editor (*e.g.*, emacs).
  3. Re-assign the following parameters: *waveform: -1*, *baro: 3*, *dncm: 1*, *breathing: 1*, *dra: 1*, and *df: 1*.
  4. Save the file *parameters_4*.
  5. Run the following command at the Linux prompt:
     rcvsim parameters_4 foo4
  6. Any time after the completion of the previous step, execute the following command at the Linux prompt:
     wave -r foo4 -s 1 15 26 -a qrs

  Or, if **Ex. 3** have been previously implemented, then

  1. Execute the following command at the Linux prompt:
     wave -r foo3 -s 1 15 26 -a qrs
- *Execution Output:*
  - If **Ex. 3** has not been previously implemented, then the following files will be created in the current directory: *foo4.dat*, *foo4.qrs*, *foo4.hea*, and *parameters_4.0*.
  - When the *wave* executable is implemented, a WAVE window will appear. The researcher may then use the arrow buttons at the top of the WAVE display system to scroll through the 300 seconds of generated waveforms with annotations. Figure 12 will appear after clicking the forward double arrow button twice or by directly running the *wave* executable with the following additional argument: *-f 40*.

Ex. 5

- *Desired Execution:*
  - On-line display of systemic arterial pressure and volume with annotations.
  - Uncontrolled, unperturbed, intact pulsatile heart and circulation initially with default parameter values.
  - On-line reduction in systemic arterial compliance by a factor of two.

- *Required Steps:*

  1. Copy file *$DIR/bin/parameters.def* to the current directory with the new file name *parameters_5*.
  2. Open the file *parameters_5* with any text editor (*e.g.*, emacs).
  3. Re-assign the following parameter: *waveform: 1 10*. Make sure all of the status parameters are assigned the numerical value of zero.
  4. Save the file *parameters_5*.
  5. Run the following command at the Linux prompt:
     rcvsim parameters_5 foo5
  6. Some time in the midst of the simulation, type "p" followed by <RETURN> at standard input.
  7. Re-assign the the following parameter: *Ca: 0.8*.
  8. Save the file *parameters_5*.
  9. Type "r" followed by <RETURN> at standard input.

- *Execution Output:*

  – A WAVE window will appear and will automatically scroll through the simulated data with annotations. The automatic scrolling will stop once Step 6. is executed. (At this point, the researcher may scroll backwards with the the arrow buttons at the top of the WAVE display system.) After Steps 7.-9. are executed, automatic scrolling will resume until a total of 300 seconds of data have been calculated. Figure 13 illustrates the WAVE window during the time of reduction in systemic arterial compliance. Note that this reduction is annotated with the name of the saved parameter file. (Also note how systemic arterial volume is conserved through the instantaneous change in systemic arterial pressure.)

  – The following files will be created in the current directory: *foo5.dat*, *foo5.qrs*, *foo5.hea*, *parameters_5.0*, and *parameters_5.1*.

Ex. 6

- *Desired Execution:*

  – On-line display of systemic arterial pressure, intrathoracic pressure, and instantaneous lung volume with annotations.

  – Uncontrolled, intact pulsatile heart and circulation initially with default parameter values perturbed by only fixed-rate breathing.

  – First, an on-line reduction in lung compliance by a factor of two. Then, an on-line, 500 ml step increase in the functional reserve volume of the lungs.

- *Required Steps:*

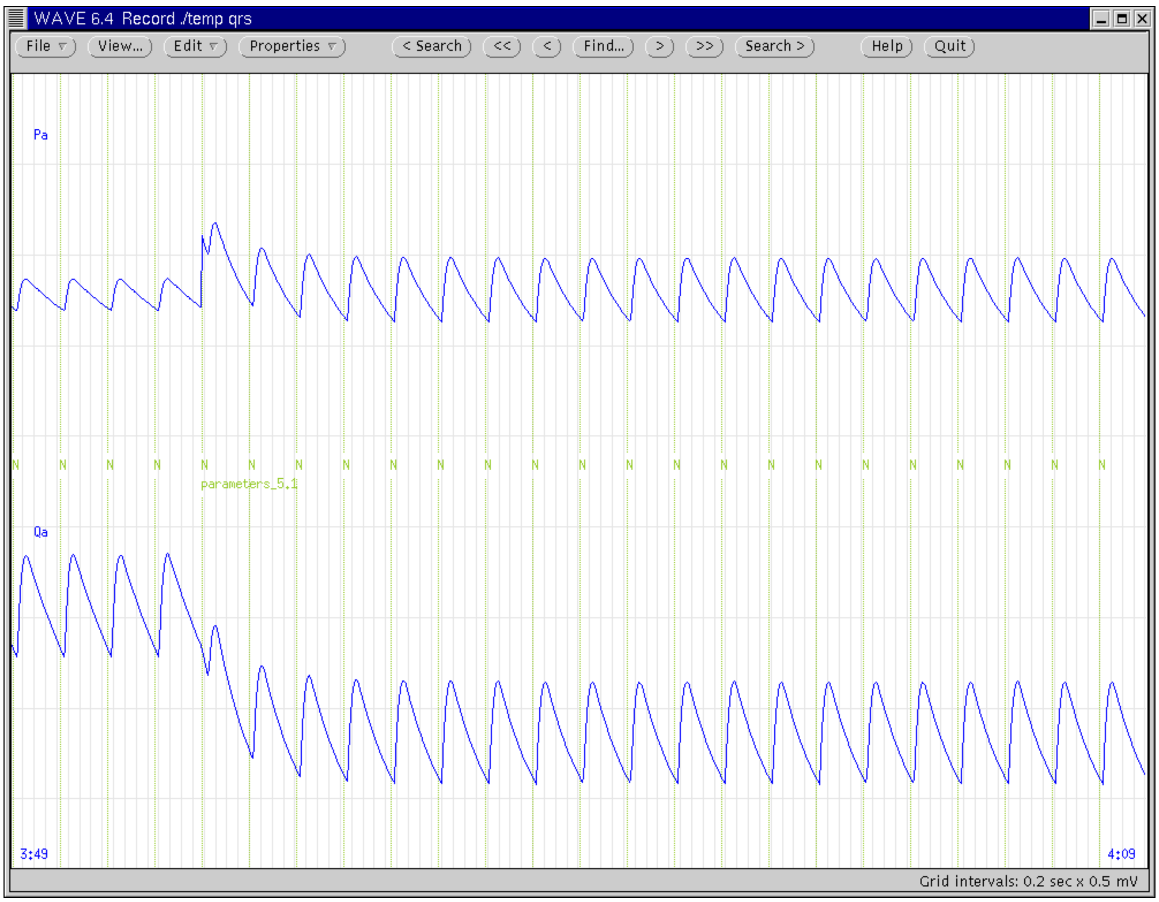


Figure 13: WAVE window generated according to Ex. 5.

1. Copy file *$DIR/bin/parameters.def* to the current directory with the new file name *parameters_6*.
2. Open the file *parameters_6* with any text editor (*e.g.*, emacs).
3. Re-assign the following parameters: *waveform: 1 6 15* and *breathing: 1*.
4. Save the file *parameters_6*.
5. Run the following command at the Linux prompt:
   rcvsim parameters_6 foo6
6. Some time in the midst of the simulation, type "p" followed by <RETURN> at standard input.
7. Re-assign the the following parameter: *Clu: 126.25*.
8. Save the file *parameters_6*.
9. Type "r" followed by <RETURN> at standard input.
10. At a subsequent time during the simulation, type "p" followed by <RETURN> at standard input.
11. Re-assign the the following parameter: *Qfrs: 500*.
12. Save the file *parameters_6*.
13. Type "r" followed by <RETURN> at standard input.

- *Execution Output:*
  - A WAVE window will appear and will automatically scroll through the simulated data with annotations. The automatic scrolling will stop once Step 6. is executed. After Steps 7.-9. are executed, automatic scrolling will resume until Step 10. has been executed. When Steps 11.-13. are executed, the automatic scrolling will resume until a total of 300 seconds of data have been simulated. Figure 14 illustrates the WAVE window during the reduction in lung compliance. (Note that this reduction does not alter instantaneous lung volume; see Section 5.3.2). Figure 15 illustrates the WAVE window during the time of the step increase in the functional reserve volume of the lungs. (Note that the step increase occurs once the current respiratory cycle is complete.)
  - The following files will be created in the current directory: *foo6.dat*, *foo6.qrs*, *foo6.hea*, *parameters_6.0*, *parameters_6.1*, and *parameters_6.2*.

Ex. 7

- *Desired Execution:*
  - On-line display of systemic arterial pressure and heart rate with annotations.
  - Uncontrolled, unperturbed, intact pulsatile heart and circulation initially with default parameter values.

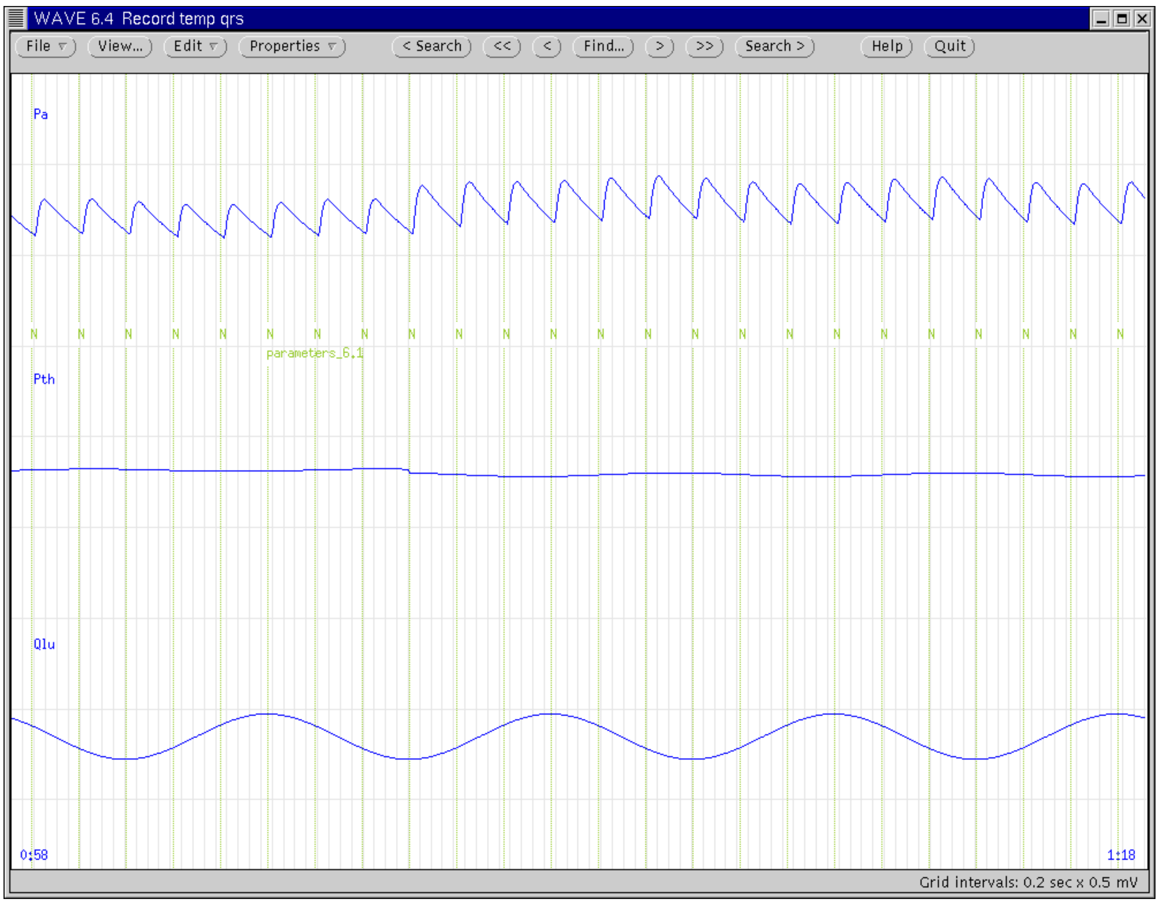


Figure 14: WAVE window generated according to the first parameter update of Ex. 6.

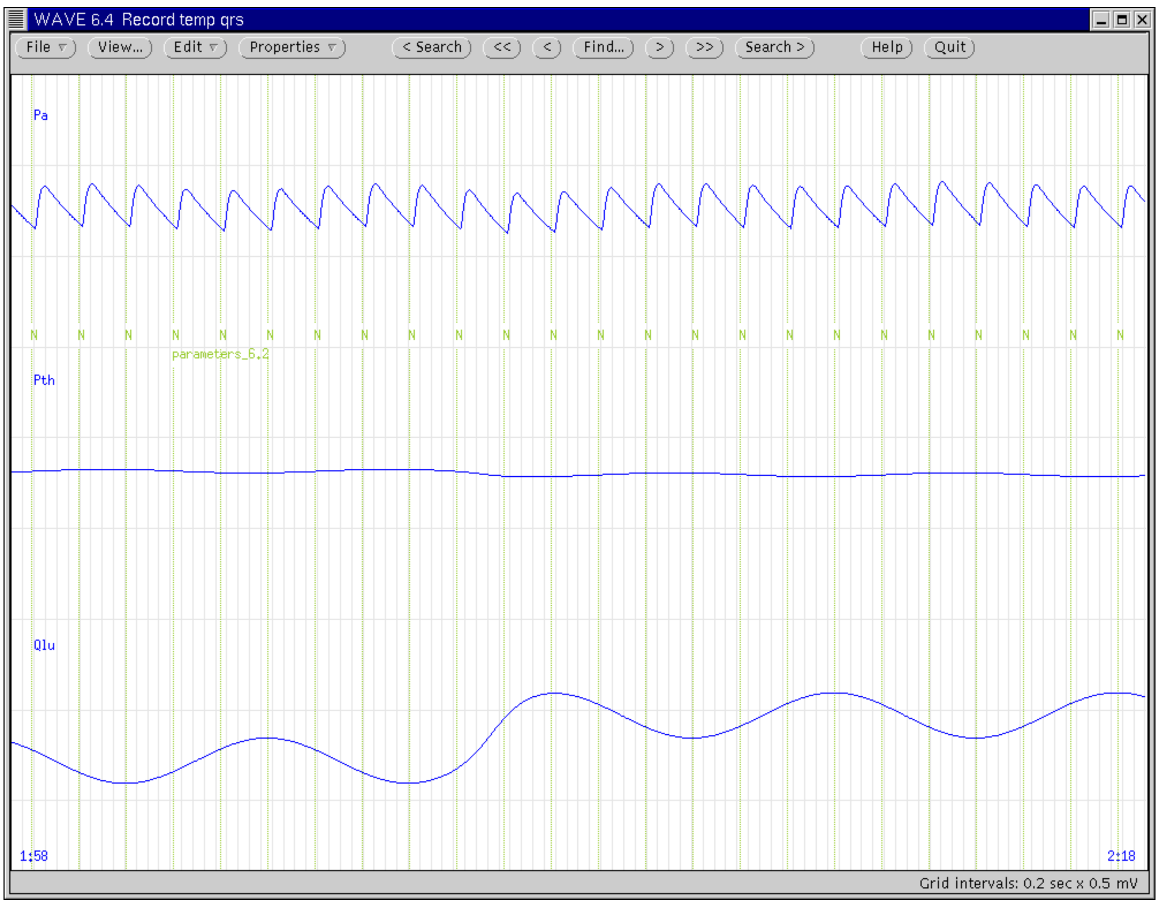


Figure 15: WAVE window generated according to the second parameter update of Ex. 6.

- First on-line hemmorhage of 500 ml. Then, on-line initiation of arterial and cardiopulmonary baroreflex control.

- *Required Steps:*

  1. Copy file *$DIR/bin/parameters.def* to the current directory with the new file name *parameters_7*.
  2. Open the file *parameters_7* with any text editor (*e.g.*, emacs).
  3. Re-assign the following parameters: *waveform: 1 26*, *baro: 3*, *bgain: 0*, *again: 0*, and *pgain: 0*.
  4. Save the file *parameters_7*.
  5. Run the following command at the Linux prompt:
     rcvsim parameters_7 foo7
  6. Some time in the midst of the simulation, type "p" followed by <RETURN> at standard input.
  7. Re-assign the the following parameter: *Qtot: 4500*.
  8. Save the file *parameters_7*.
  9. Type "r" followed by <RETURN> at standard input.
  10. At a subsequent time during the simulation, type "p" followed by <RETURN> at standard input.
  11. Re-assign the the following parameters: *bgain: 1*, *again: 1*, and *pgain: 1*.
  12. Save the file *parameters_7*.
  13. Type "r" followed by <RETURN> at standard input.

- *Execution Output:*

  - A WAVE window will appear and will automatically scroll through the simulated data with annotations. The automatic scrolling will stop once Step 6. is executed. After Steps 7.-9. are executed, automatic scrolling will resume until Step 10. has been executed. When Steps 11.-13. are executed, the automatic scrolling will resume until a total of 300 seconds of data have been simulated. Figure 16 illustrates the WAVE window once the simulation is complete. The *Time variable* of the WAVE window is set such that the waveforms over the entire simulation period may be viewed all at once. (Note how systemic arterial pressure has been returned to near normal values with the baroreflex systems.)
  - The following files will be created in the current directory: *foo7.dat*, *foo7.qrs*, *foo7.hea*, *parameters_7.0*, *parameters_7.1*, and *parameters_7.2*.

Ex. 8

- *Desired Execution:*

Figure 16: WAVE window generated according to Ex. 7 in which the time duration of the window has been expanded to illustrate the entire simulation period.

- On-line display of a cardiac output curve.
- On-line display of systemic arterial and venous pressure and left ventricle flow rate.
- Uncontrolled, unperturbed, heart-lung unit preparation with default parameter values.

- *Required Steps:*

1. Copy file *$DIR/bin/parameters.def* to the current directory with the new file name *parameters_8*.
2. Open the file *parameters_8* with any text editor (*e.g.*, emacs).
3. Re-assign the following parameters: *time: 1000*, *waveform: 1 2 17*, *preparation: 1*, *Pas: 1000*, and *Pvs: 2*.
4. Save the file *parameters_8*.
5. Run the following command at the Linux prompt:
   rcvsim parameters_8 foo8

- *Execution Output:*

  - A WAVE window will appear and will automatically scroll through the simulated data as they are being calculated until the entire cardiac output curve has been measured. Figure 17 illustrates the WAVE window at the end of the simulation. (As is always the case with viewing waveforms on-line, the parameter values may be updated prior to simulation termination, if desired.)
  - Then, the Gnuplot window of Figure 18 will appear immediately following the calculation of the entire cardiac output curve.
  - The following files will be created in the current directory: *foo8.dat*, *foo8.qrs*, *foo8.hea*, *foo8.txt* and *parameters_8.0*.

Ex. 9

- *Desired Execution:*

  - On-line display of a venous return curve.
  - Uncontrolled, unperturbed, systemic circulation preparation with default parameter values.

- *Required Steps:*

1. Copy file *$DIR/bin/parameters.def* to the current directory with the new file name *parameters_9*.
2. Open the file *parameters_9* with any text editor (*e.g.*, emacs).
3. Re-assign the following parameters: *time: 1000*, *waveform: -1*, *preparation: 2*, and *Crds: 5*.
4. Save the file *parameters_9*.

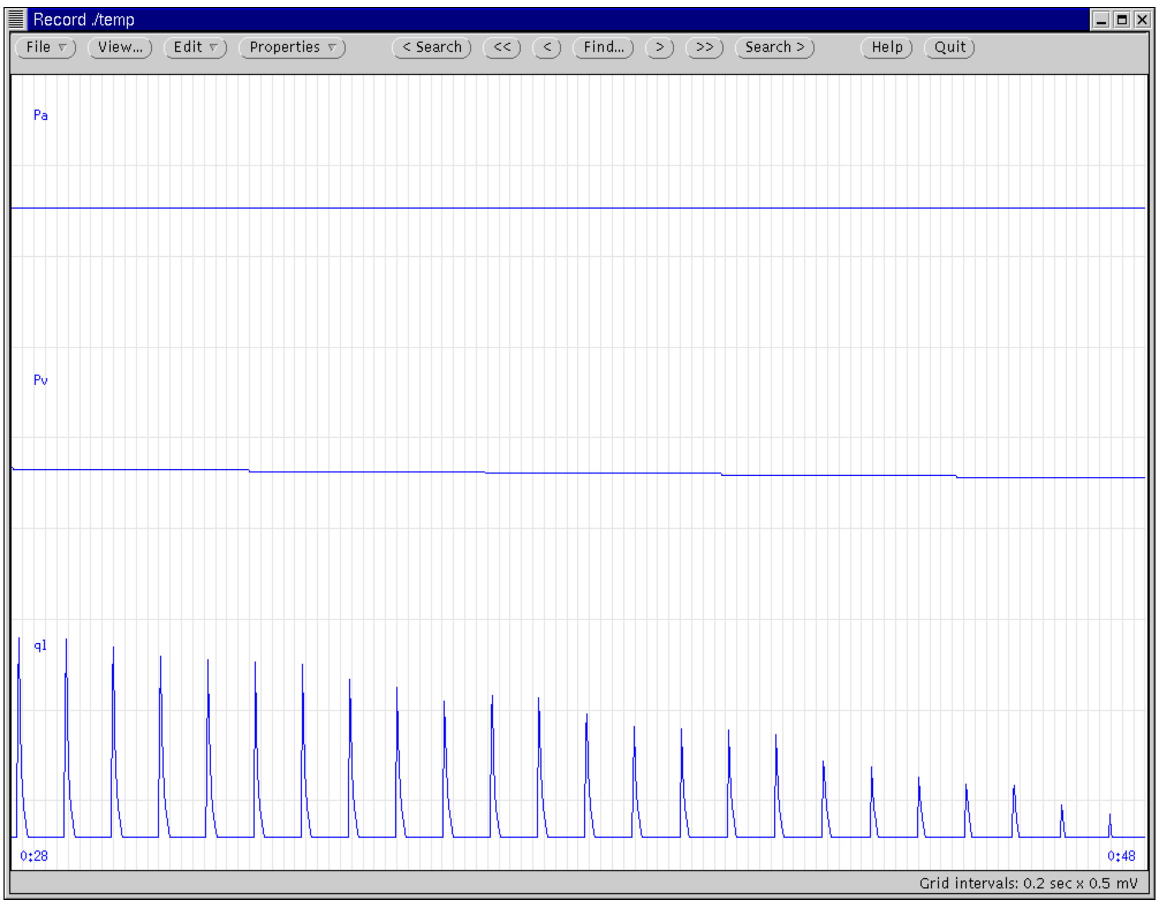


Figure 17: WAVE window generated according to Ex. 8.

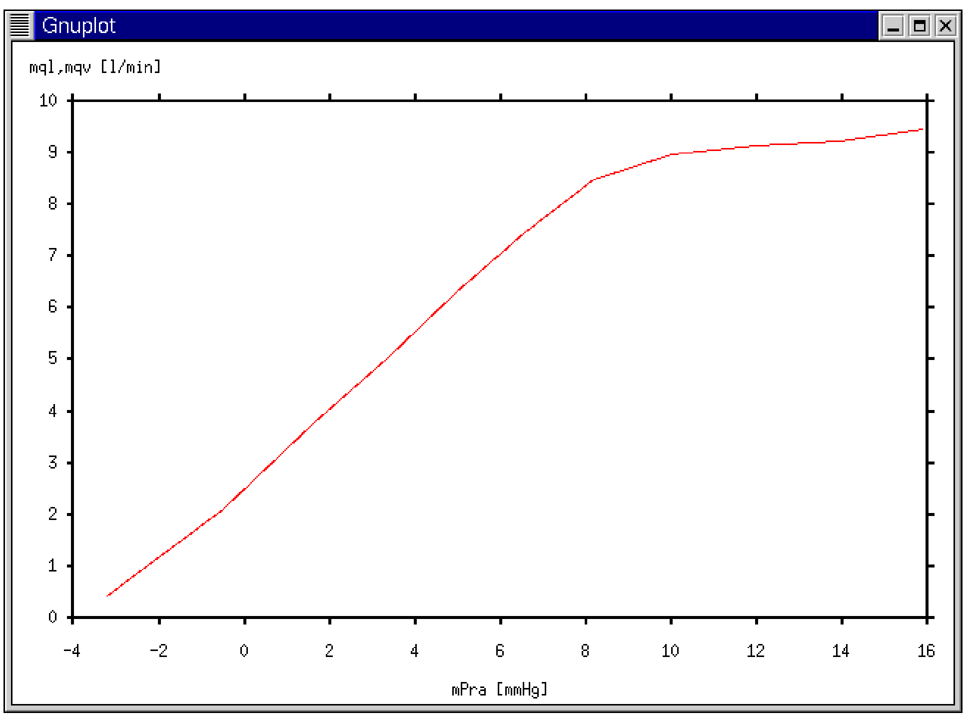


Figure 18: Gnuplot window generated according to Ex. 8, Ex. 10, and Ex. 11.

5. Run the following command at the Linux prompt:
   rcvsim parameters_9 foo9

- *Execution Output:*
  - The Gnuplot window of Figure 19 will appear immediately following the calculation of the entire venous return curve.
  - The following files will be created in the current directory: *foo9.dat*, *foo9.qrs*, *foo9.hea*, *foo9.txt* and *parameters_9.0*.

Ex. 10

- *Desired Execution:*
  - On-line display of multiple cardiac output and venous return curves.
  - Uncontrolled, unperturbed, heart-lung unit and systemic circulation preparations with default parameter values and after a 25% increase in systemic arterial resistance, mean systemic pressure, heart rate, and contractility.
- *Required Steps:*
  1. Copy file *$DIR/bin/parameters.def* to the current directory with the new file name *parameters_10*.
  2. Open the file *parameters_10* with any text editor (*e.g.*, emacs).
  3. Re-assign the following parameters: *time: 1000*, *waveform: -1*, *preparation: 1*, *Pas: 1000*, and *Pvs: 2*.
  4. Save the file *parameters_10*.
  5. Run the following command at the Linux prompt:
     rcvsim parameters_10 foo10a
  6. Once the simulation is complete, re-assign the following parameters: *numerics: 1*, *preparation: 2*, and *Crds: 5*.
  7. Save the file *parameters_10*.
  8. Run the following command at the Linux prompt:
     rcvsim parameters_10 foo10b
  9. Once the simulation is complete, re-assign the following parameters: *Ra: 1.25* and *Pms: 8.625*.
  10. Save the file *parameters_10*.
  11. Run the following command at the Linux prompt:
      rcvsim parameters_10 foo10c
  12. Once the simulation is complete, re-assign the following parameters: *preparation: 1*, *Cls: 0.3*, *Crs: 0.9*, and *F: 1.5*.
  13. Save the file *parameters_10*.

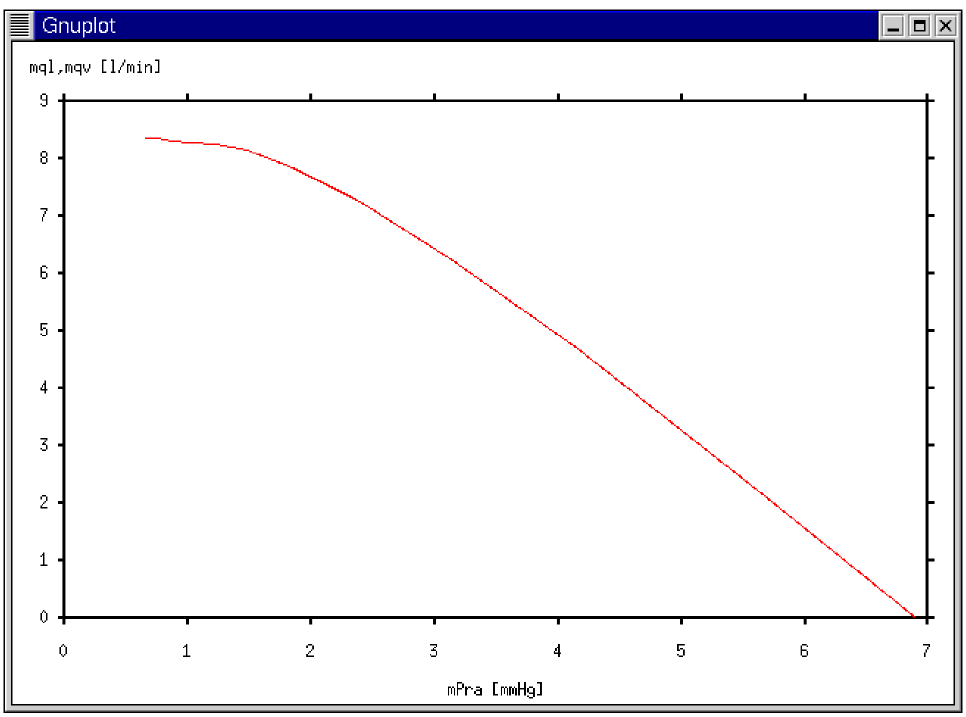


Figure 19: Gnuplot window generated according to Ex. 9.

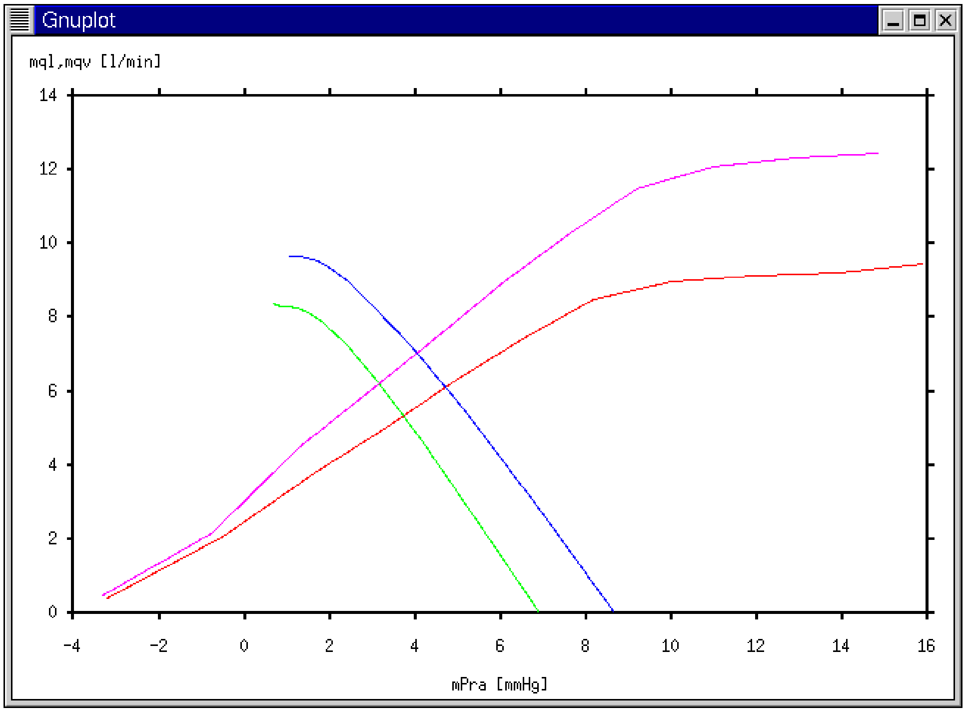


Figure 20: Gnuplot window generated according to Ex. 10 and Ex. 11.

14. Run the following command at the Linux prompt:
    rcvsim parameters_10 foo10d

- *Execution Output:*
    - A total of four Gnuplot windows will be displayed beginning with a window displaying a single cardiac output curve (see Figure 18); then a window displaying the previous cardiac output curve with a venous return curve; followed by a window displaying these two previous curves with another venous return curve which is enhanced; and ending with a window displaying each of these three curves and an additional enhanced cardiac output curve (see Figure 20). (Note the increase in average cardiac output that occurs due to the enhancement of the curves.) Each of the four windows will appear immediately after the completion of each of the four *rcvsim* executions (Steps 5., 8., 11., 14.).
    - The following files will be created in the current directory: *foo10a.dat*, *foo10a.qrs*, *foo10a.hea*, *foo10a.txt*, *foo10b.dat*, *foo10b.qrs*, *foo10b.hea*, *foo10b.txt*, *foo10c.dat*, *foo10c.qrs*, *foo10c.hea*, *foo10c.txt*, *foo10d.dat*, *foo10d.qrs*, *foo10d.hea*, *foo10d.txt* and *parameters_10.0*.

Ex. 11

- *Desired Execution:*

– Off-line display of the cardiac output and venous return curves generated from Ex. 10.

- *Required Steps:*

1. Change directory to that which contains the simulated data of Ex. 10.
2. Run *gnuplot* at the Linux prompt.
3. At the Gnuplot prompt, enter the following commands:
set tics out
set xlabel 'mPra [mmHg]'
set ylabel 'mql,mqv [l/min]'
plot 'foo10a.txt' using 1:2 notitle with lines
replot 'foo10b.txt' using 1:2 notitle with lines
replot 'foo10c.txt' using 1:2 notitle with lines
replot 'foo10d.txt' using 1:2 notitle with lines
(Note that the plot command is similar to *numerics: 0*, while the replot command is analogous to *numerics: 1*.)

- *Execution Output:*

– A total of four Gnuplot windows will be displayed beginning with a window displaying a single cardiac output curve (see Figure 18); then a window displaying the previous cardiac output curve with a venous return curve; followed by a window displaying these two previous curves with another venous return curve which is enhanced; and ending with a window displaying each of these three curves and an additional enhanced cardiac output curve (see Figure 20).

Ex. 12

- *Desired Execution:*

– On-line display of average cardiac output as a function of average systemic arterial pressure.

– Uncontrolled, unperturbed, heart-lung unit preparation with default parameter values.

- *Required Steps:*

1. Copy file *$DIR/bin/parameters.def* to the current directory with the new file name *parameters_12*.
2. Open the file *parameters_12* with any text editor (*e.g.*, emacs).
3. Re-assign the following parameters: *time: 1000*, *waveform: -1*, *numerics: 2*, *preparation: 1*, *Pas: 30*, and *Pvs: 100*.
4. Save the file *parameters_12*.
5. Run the following command at the Linux prompt:
rcvsim parameters_12 foo12

- *Execution Output:*
  - The Gnuplot window of Figure 21 will appear immediately following the calculation of the entire curve.
  - The following files will be created in the current directory: *foo12.dat*, *foo12.qrs*, *foo12.hea*, *foo12.txt* and *parameters_12.0*.

Ex. 13

- *Desired Execution:*
  - Off-line display of the curve of average cardiac output as a function of average systemic arterial pressure generated from Ex. 12.
- *Required Steps:*
  1. Change directory to that which contains the simulated data of Ex. 12.
  2. Run *gnuplot* at the Linux prompt.
  3. At the Gnuplot prompt, enter the following commands:
     set tics out
     set xlabel 'mPa [mmHg]'
     set ylabel 'mql [l/min]'
     plot 'foo12.txt' using 3:2 notitle with lines
- *Execution Output:*
  - The Gnuplot window of Figure 21 will again appear.

6 A Research Example

The human cardiovascular model upon which *RCVSIM* is based was originally constructed in order to advance research in the general area of beat-to-beat hemodynamic variability [?, 4, 8]. The *RCVSIM* software enhances the potential of the original human cardiovascular model in facilitating cardiovascular research by making the model more user friendly and compatible with the open-source software provided by PhysioNet. By further disseminating *RCVSIM* to the cardiovascular research community through PhysioNet, researchers may conveniently utilize the computational model to complement their studies with the experimental data sets available on PhysioNet. For example, *RCVSIM* has been previously utilized to develop an algorithm for monitoring systemic arterial resistance from only a peripheral arterial pressure waveforms which was subsequently validated with data from the MIMIC database on PhysioNet [4]. Another research example which illustrates how *RCVSIM* may be utilized in conjunction with the open-source software and experimental data sets of PhysioNet in order to improve the accuracy of the model, and thus possibly physiologic understanding, is provided below.

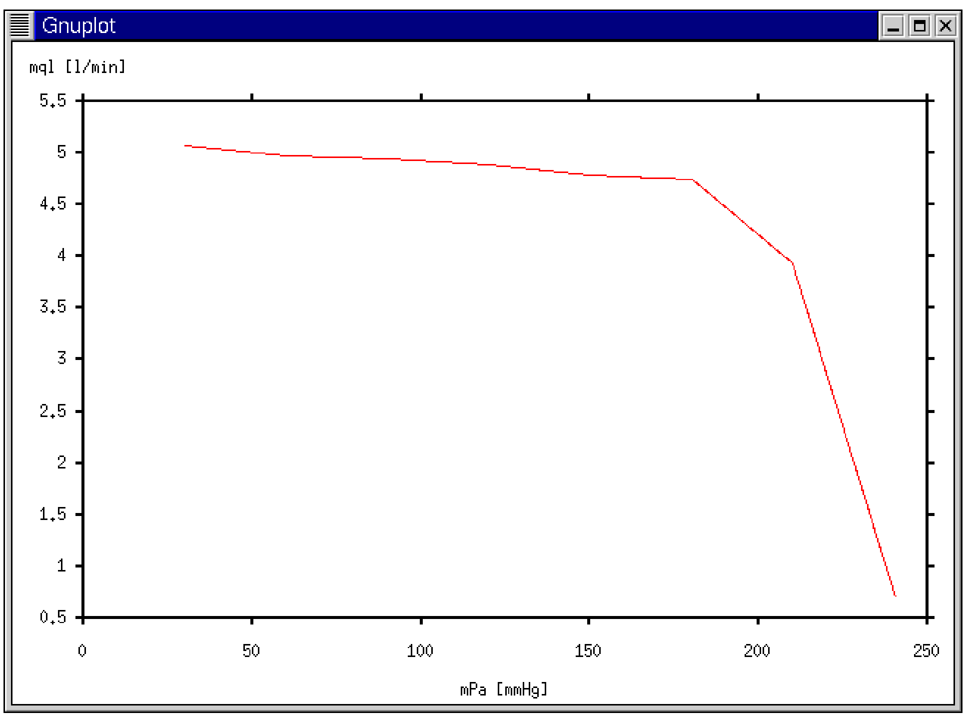


Figure 21: Gnuplot window generated according to Ex. 12 and Ex. 13.

The default or nominal parameter values of the human cardiovascular model are set such that the power spectra of the simulated beat-to-beat hemodynamic variability resembles power spectra measured from a group of normal humans in the *standing* posture [4, 5]. The objective of the research example here is to determine a set of parameter values which permit the model to generate a realistic *supine* posture, heart rate power spectrum. In order to address this objective, it is necessary to obtain experimental data sets to define what is realistic and software to compute the heart rate power spectrum – both of which are available from PhysioNet. The specific steps which were implemented to achieve the research objective are given below.

1. Establish realistic supine posture, heart rate power spectrum.

   (a) Visit the following web page:
   http://www.physionet.org/physiobank/database/meditation/data/
   which houses Exaggerated Heart Rate Oscillations During two Meditation Techniques: Data.

   (b) Download the data in the metronomic breathing group from the bottom of this web page – *M#.hea* and *M#.qrs*, where # ranges from 1 to 14. (These data provide the qrs times of 14 volunteer subjects in the supine posture breathing at a fixed-rate of 0.25 Hz.)

   (c) Calculate an instantaneous heart rate tachogram from the qrs times for each subject by executing the following command at the Linux prompt (14 times):
   tach -r M# -a qrs -f > hr#
   (Note that tach is open-source software provided by PhysioNet. Type *tach -h* at the Linux prompt for help.)

   (d) Calculate the maximum entropy power spectrum of the instantaneous heart rate tachogram for each subject by executing the following command at the Linux prompt (14 times):
   memse -f 2 -Z -o 15 hr# > phr#
   (Note that memse is open-source software provided by PhysioNet. Type *memse -h* at the Linux prompt for help. The generated files *phr#* are two-column, ASCII format files in which the first column represents frequencies and the second column represents the corresponding power spectral densities.)

   (e) Average the power spectra over the 14 subjects and write the averaged spectra to a two-column ASCII file called *avephr* (by writing a simple program or using any pre-existing software such as MATLAB).

   (f) Plot the averaged power spectrum by executing the following command at the Linux prompt:
   plot2d avephr 0 1
   (Note that plot2d, which is a simple program that controls Gnuplot, is open-source software provided by PhysioNet. Type *plot2d -h* at the Linux prompt for help.)

2. Determine model parameter values which permit the model and averaged, experimental heart rate power spectra to match.

   (a) Copy file *$DIR/bin/parameters.def* to the current directory with the new file name *parameters_r*.

(b) Open the file *parameters_r* with any text editor (*e.g.*, emacs).

(c) Re-assign the following parameters: *waveform: -1*, *baro: 3*, *dncm: 1*, *breathing: 1*, *dra: 1*, *df: 1*, *Tr: 4*, and *Qt: 430*. (Since accompanying experimental respiratory data is not available, the last parameter is arbitrarily set such that the alveolar ventilation rate is 70 ml/s.)

(d) Save the file *parameters_r*.

(e) Execute the following commands at the Linux prompt:
rcvsim parameters_r foor
tach -r foor -a qrs -f > hrsim
memse -f 2 -Z -o 15 hrsim > phrsim
plot2d phrsim 0 1

(f) If this plot matches the experimental plot above, then the research objective has been achieved. Otherwise, re-assign the following parameters: *bgain*, *again*, *pgain*, *stdwr*, and *stdwf*, and repeat the steps above beginning with Step (d). (Note that these five parameters have been identified based on a priori knowledge of the physiologic differences between supine and standing postures.)

When the values assigned to the parameters of Step (f) are set as follows: *bgain: 0.5*, *again: 0.5*, *pgain: 1*, *stdwr: 0.04*, and *stdwf: 0.175*, the averaged experimental and model supine posture, heart rate power spectra match (see Figure 22). As expected, the parameter changes from the standing posture to supine posture reflected a shift in autonomic balance favoring the parasympathetic nervous system. Interestingly, a further comparison of these parameter values with the nominal values suggests that the posture peak in humans ($\sim$0.1 Hz [10]; present in the model with default parameter values) could be due to both a system resonance which is established by increased sympathetic nervous activity as well as increased fluctuations in local vascular resistance beds which may be due to increased leg muscle activity.

A Other Models

In addition to the models of Section 2, other lumped parameter models of the pulsatile heart and circulation and resting physiologic perturbation models may be implemented with the *RCVSIM* source code. These models may only be implemented at the MATLAB prompt by executing *simulate.mexlx*. A brief description of each of these models and the relevant MATLAB functions is given below.

- Lumped parameter models of the pulsatile heart and circulation
  - *Left ventricle preparation.* The electrical circuit analog of this preparation may be visualized by replacing C_a and C_{pv} in Figure 1 with the DC voltage sources P_a and P_{pv}, respectively. This preparation may be utilized for the analysis of the input-output properties of the left ventricle model; however, there is currently no source code to alter the DC voltage sources during a *single* simulation. The initial pressure, volume, and flow rate of the preparation are computed with the function *lv_init_cond.m*, and

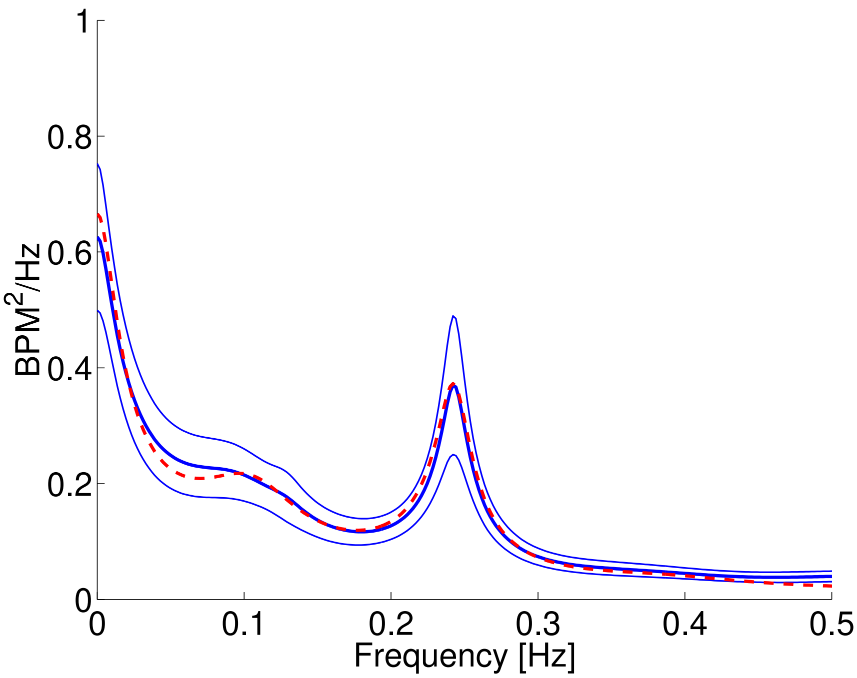


Figure 22: Model (red) and experimental (blue) supine posture, heart rate power spectra at fixed-rate breathing of 0.25 Hz. The dark blue line is the average spectrum computed from 14 volunteers, while the two lighter blue lines are the corresponding 95% confidence intervals. See text for additional details.

the derivative of the pressure at a desired time step is determined with the function *lv_eval_deriv.m*.

- *Intact circulatory preparation for measurement of single ventricular contraction $P_a(t)$ response.* The electrical circuit analog of this preparation is given by Figure 1and includes an additional parameter (nve) which represents the beat number after which the ventricles will no longer contract. The single ventricular contraction $P_a(t)$ response may then be determined by executing the preparation for nve, and then nve-1, ventricular contractions and then taking the difference between the two resulting $P_a(t)$ waveforms.
- *Intact circulatory preparation with only linear elements.* The electrical circuit analog of this preparation is given by Figure 1 in which the four nonlinear elements are replaced by purely linear elements. This model was previously presented by Davis [3]. The initial pressures, volumes, and flow rates of the preparation are computed with the function *init_cond.m*, and the derivative of the pressures at a desired time step is determined with the function *eval_deriv.m*.
- *Intact circulatory preparation with third-order systemic arteries.* The electrical circuit analog of this preparation may be visualized by replacing the capacitor C_a in Figure 1 with two grounded capacitors connected via an inductor. The capacitor proximal to the left ventricle compartment represents the large, elastic (e) arteries, the other capacitor represents the small, muscular (m) arteries, and the inductor (L_e) accounts for the inertial effects of blood flow between the two lumped arteries. This third-order model of the systemic arteries was previously presented by Clark [2]. The $P_m(t)$ waveform may be considered as a first-order approximation of a peripheral arterial blood pressure waveform. The initial pressures, volumes, and flow rates of the preparation are computed with the function *third_init_cond.m*, and the derivative of the pressures at a desired time step is determined with the function *third_eval_deriv.m*.
- *Intact circulatory preparation with nonlinear systemic arterial compliance.* The electrical circuit analog of this preparation is given by Figure 1 with a box encompassing C_a to denote its nonlinearity. This nonlinear element is characterized by the curvature (K), differential compliance (C_a), and volume (Q_{nac}) all at P_a^{sp}. Provided that $K < 0$, the differential compliance decreases with increasing $P_a(t)$. The initial pressures, volumes, and flow rates of the preparation are computed with the function *nac_init_cond.m*, and the derivative of the pressures at a desired time step is determined with the function *nac_eval_deriv.m*.
- *Intact circulatory preparation with third-order systemic arteries and nonlinear, large elastic arterial compliance.* This preparation is a combination of the previous two preparations with a nonlinear C_e and linear C_m. The initial pressured, volumes, and flow rates of the preparation are computed with the function *third_nac_init_cond.m*, and the derivative of the pressures at a desired time step is determined with the function *third_nac_eval_deriv.m*.
- *Intact circulatory preparation with an arterial pressure reservoir preparation.* The electrical circuit analog of this preparation may be visualized by replacing C_a in Figure 1 with a DC voltage source P_a. This preparation may be utilized to understand

hemodynamics while $P_a(t)$ is held constant. The initial pressures, volumes, and flow rates of the preparation are computed with the function *apr_init_cond.m*, and the derivative of the pressures at a desired time step is determined with the function *apr_eval_deriv.m*.

  - *Intact circulatory preparation with contracting atria.* The electrical circuit analog of this preparation may be visualized by inserting right atrial (ra) and left atrial (la) compartments (linear resistor and linear, variable capacitor with an unstressed volume) between the venous and ventricular compartments in Figure 1. The atrial and ventricular compliances at a desired time step are respectively computed by the functions *var_vcap.m* and *var_acap.m*. The initial pressures, volumes, and flow rates of the preparation are computed with the function *a_init_cond.m*, and the derivative of the pressures at a desired time step is determined with the function *a_eval_deriv.m*.

- Resting physiologic perturbations

  - *Respiratory activity.* In addition to fixed-rate breathing and random-interval breathing with varying tidal volumes, $Q_{lu}(t)$ may also be represented as a step or impulse of desired amplitude or area (*Qfrs*) and at a desired time (*Qfrt*) as well as at random-intervals with a *constant* tidal volume. These breathing patterns are generated with the function *resp_act.m*.
  - *Autoregulation of local vascular beds.* In addition to bandlimited white noise, autoregulation of local vascular beds may also be represented as bandlimited, *1/f* noise or a sinusoid of desired amplitude (*ar*) and frequency (*fr*). The former representation is generated with the functions *bl_filt.m* and *oneoverf_filt.m*.
  - *Central oscillator.* A central oscillator is represented as an exogenous, sinusoidal disturbance to P_a^{sp} of desired amplitude (*ap*) and frequency (*fp*).
  - *Non-baroreflex mediated fluctuations in $Q_v^0(t)$.* Fluctuations in $Q_v^0(t)$ not due to the baroreflexes are represented as a white disturbance of desired standard deviation (*stdwq*) that is bandlimited to a desired frequency ($fcoq$). These fluctuations may specifically be due to, for example, fast acting hormonal loops. These fluctuations are generated with the function *bl_filt.m*.

In order to implement all of the above models, rather than using *read_param.m*, the parameter vector *th* must be created by first copying the file *$DIR/bin/header_def.m* to the current directory and then executing *th=header_def;* at the MATLAB prompt (Note that *header_def.m* can be copied to any name as long as it has the extension *.m*). Additionally, the appropriate option of the arguments to *simulate.mexlx* (type *help simulate* at the MATLAB prompt) must be selected.

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