

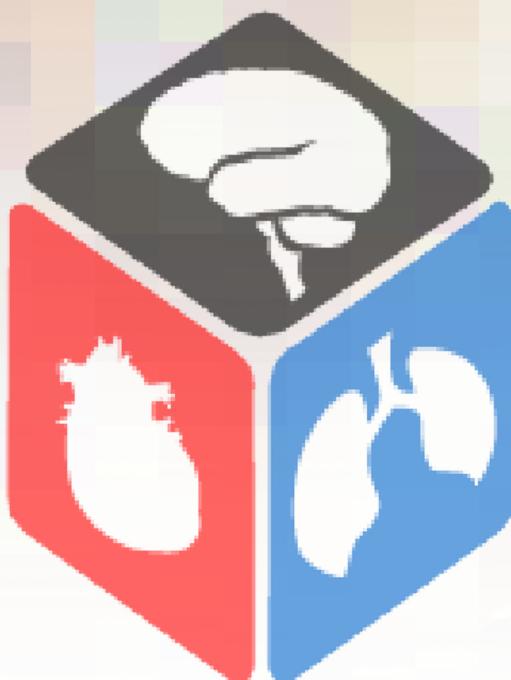
University of Southern California

Release 3.0

Simulation of State-
CardioRespiratory Interactions

PNEUMA

Biomedical Simulations Resource (BMSR)



by
**Limei Cheng, Ph.D.,
Olga Ivanova, Ph.D.,
Hsing-Hua Fan, Ph.D.**

and
Michael C.K. Khoo, Ph.D.

User's Guide

BMSR
BIOMEDICAL
SIMULATIONS
RESOURCE
bmsr.usc.edu

University of Southern California
Biomedical Simulations Resource (BMSR)
1042 Downey Way, DRB 367
Los Angeles, CA 90089-1111
Telephone (213) 740-0342
Fax (213) 740-0343

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PNEUMA User's Guide

Contact: pneuma.bmsr@gmail.com

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PNEUMA Release Agreement

Before you use PNEUMA, please read the following conditions for using our package. Thank you for your cooperation.

- PNEUMA is restricted to non-profit research and instructional purposes aimed at further knowledge in the area of cardiorespiratory system modeling and simulation. PNEUMA is supported by University of Southern California (USC) Biomedical Simulations Resource (BMSR) (NIH Grant P41-EB001978).
- Any publications of research results that were obtained in part by the use of PNEUMA will contain proper acknowledgement of the BMSR at USC. Reprints of such publications will be sent to the BMSR for the record.
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Getting Started

Thank you for trying out PNEUMA and its modularized component models. Before using PNEUMA, please take a moment to read the **Release Agreement** first. To download the associated files or their updates, please go to bmsr.usc.edu and click on **Software**. Before you begin to use PNEUMA or its individual model components, please take a moment to make sure that you have downloaded the most recent files that you will be using. In Appendix I, there is a full list of files that are included in zipped format on the BMSR-PNEUMA web site. After you unzip the downloaded file, please refer to the appendix and check that you have the correct files.

Individual Sub-Models

PNEUMA is implemented using Simulink and Matlab version R2007b or higher (© The Mathworks Inc., Natick, MA), which provides a graphical programming environment that promotes modularization of the overall model into hierarchically smaller subsystems. This allows the user to customize parts of the overall model in accordance to his/her simulations needs. Alternatively, the user may also choose to focus on a specific PNEUMA block and use it to study the corresponding mechanism of interest. Therefore, depending on the user's interest and needs, individual component blocks may be downloaded and used.

Please refer to the reference and the “.m” file for variable names and values of each compartment. Some of the components are difficult to decompose into smaller modules and therefore may not be suitable for your application. If you have suggestions or would like to request modifications to PNEUMA components that would better suit your simulation needs, please feel free to send us feedback. Contact information is provided in the Support and Contact section of this manual.

PNEUMA V.3.0: What's New

In Pneuma Release 3.0, we have incorporated a metabolic component with autonomic-metabolic interactions into the existing integrative comprehensive simulation model. This metabolic component of PNEUMA is based on prior models of glucose-insulin regulation by Bergman et al. (1979) and free fatty acid (FFA) regulation by Roy and Parker (2006). Changes in sympathetic activity from the autonomic portion of PNEUMA produce changes in epinephrine output, which in turn affects the metabolism of glucose, insulin and FFA. Inputs from the dietary intake of glucose and external interventions, such as insulin injections, have also been incorporated into the model. Also incorporated is autonomic “feedback” from the metabolic component to the rest of PNEUMA in the following way: changes in insulin level are assumed to lead to changes in sympathetic tone. The “Control Panel” along with other input panels have been improved to facilitate greater user interaction and control of the simulations

References

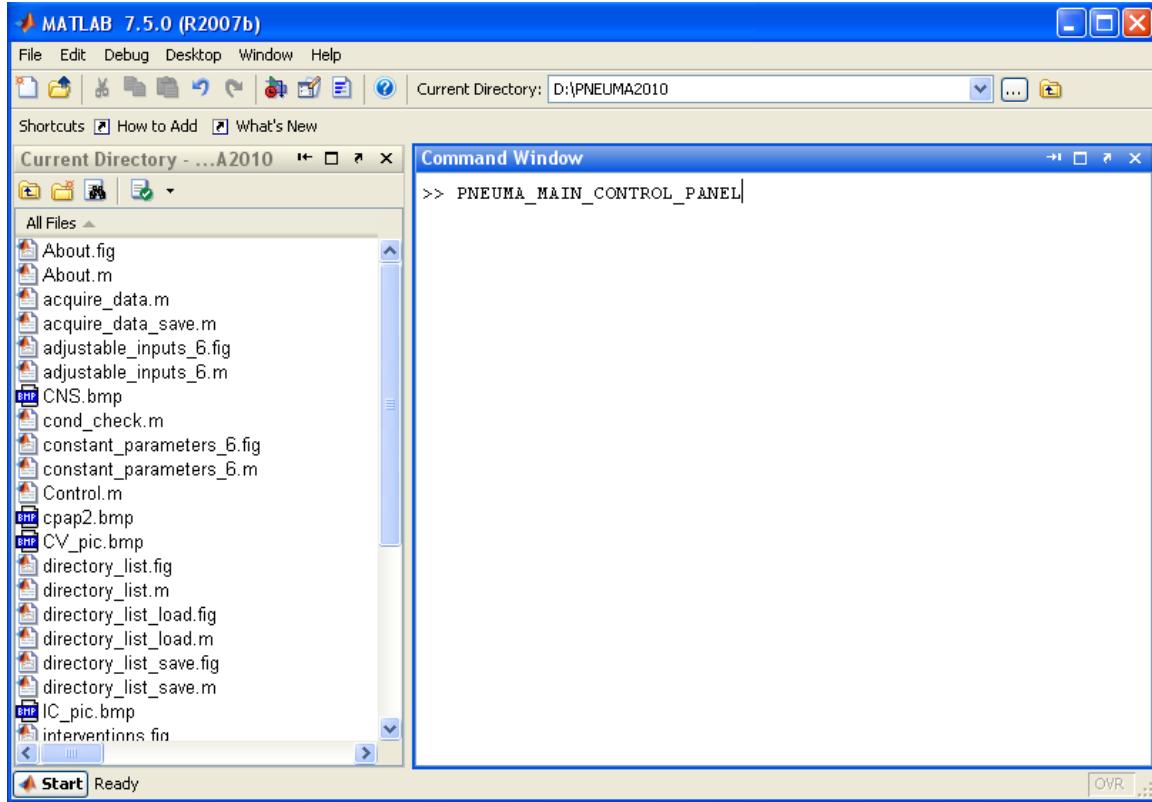
Bergman, R. N., Ider, Y. Z., Bowden, C.R.,and Cobelli,C.(1979).Quantitative estimation of insulin sensitivity. *Am. J. Physiol.* 236, E667–E677.

Roy, A., and Parker, R. S. (2006). Dynamic modeling of free fatty acid, glucose, and insulin: an extended “Minimal Model”. *Diabetes Technol. Ther.* 8, 617–626.

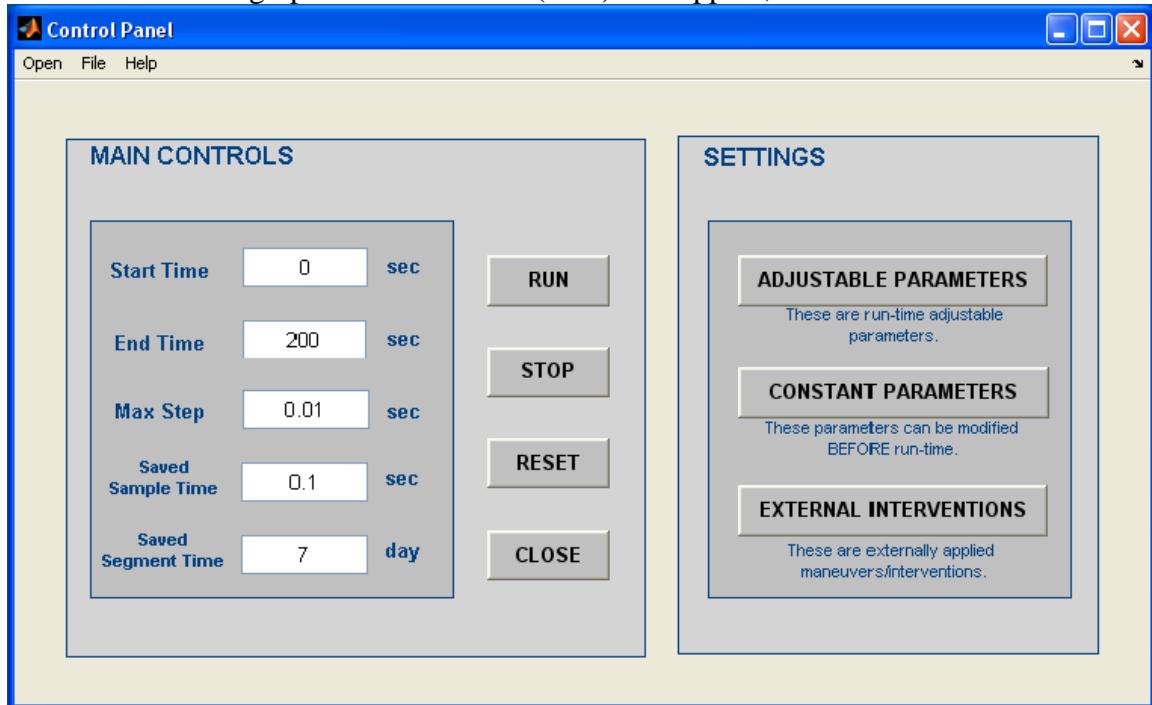
Using Pneuma

To begin using Pneuma, unzip the “**PneumaRelease3.zip**” file and check that you have all the necessary files. For the list of files in “**PneumaRelease3.zip**” file, please refer to “[Getting Started](#)” section. After you have unzipped the file and you are ready to run the program in the MATLAB environment, make sure that you are in the directory where the unzipped files are located. To Open Pneuma, in the Matlab command prompt, type “**PNEUMA_MAIN_CONTROL_PANEL**”.

If you are running Pneuma using a version of Matlab higher than Matlab75 (version 2007b), a series of warnings may appear due to compatibility issues, but these warnings should disappear after the first time you open PNEUMA.



The Control Panel graphic user interface (GUI) will appear, as shown below.



Next, input the parameter values.

- **Start Time:** time to start the simulation. (default is zero seconds)
- **End Time:** end-time (in seconds) of the simulation (for example: $3600*24*7$ will end up with 7-day simulation).
- **Max Step:** the simulation is using variable integration time steps, and it requires that the user specify the maximum allowable time step. A large max time step is not recommended (the default is 0.01 second).
- **Saved Sample Time:** some of the parameter/variable values can be saved to data files after each simulation and the user has the option of specifying the sample time of the saved segment. If given value -1, it will be default sample time of the simulation which can be used for saving data with “**Saved Segment Time**” as 0.5 day. The suggested sample time for saving is 0.1 second for neural-cardio-respiratory system. The sample time for metabolic system is constant as 6 seconds.
- **Saved Segment Time:** each data file can be saved as long as the segment time. The suggested time is 7 days.

The “**Run**” and “**Stop**” buttons allow the user to run and terminate the simulation. Currently, the Real Time Workshop allows the simulation to run using the accelerated mode even with standard Matlab Simulink package. So the “**Run**” operation will run in *accelerated mode* that allows the simulation to run faster. If the user prefers to execute the model in *normal mode*, it will have to be run under Simulink model itself rather than using that GUI button (see options under *Simulation* tab in Simulink model window). If you decide to stop the simulation before the **End Time** that you have specified, some data will be stored to files (**Saved Sample Time** option) and all the variables are in the workspace which can be saved later. The “**Reset**” button will reset all variable values to their defaults.

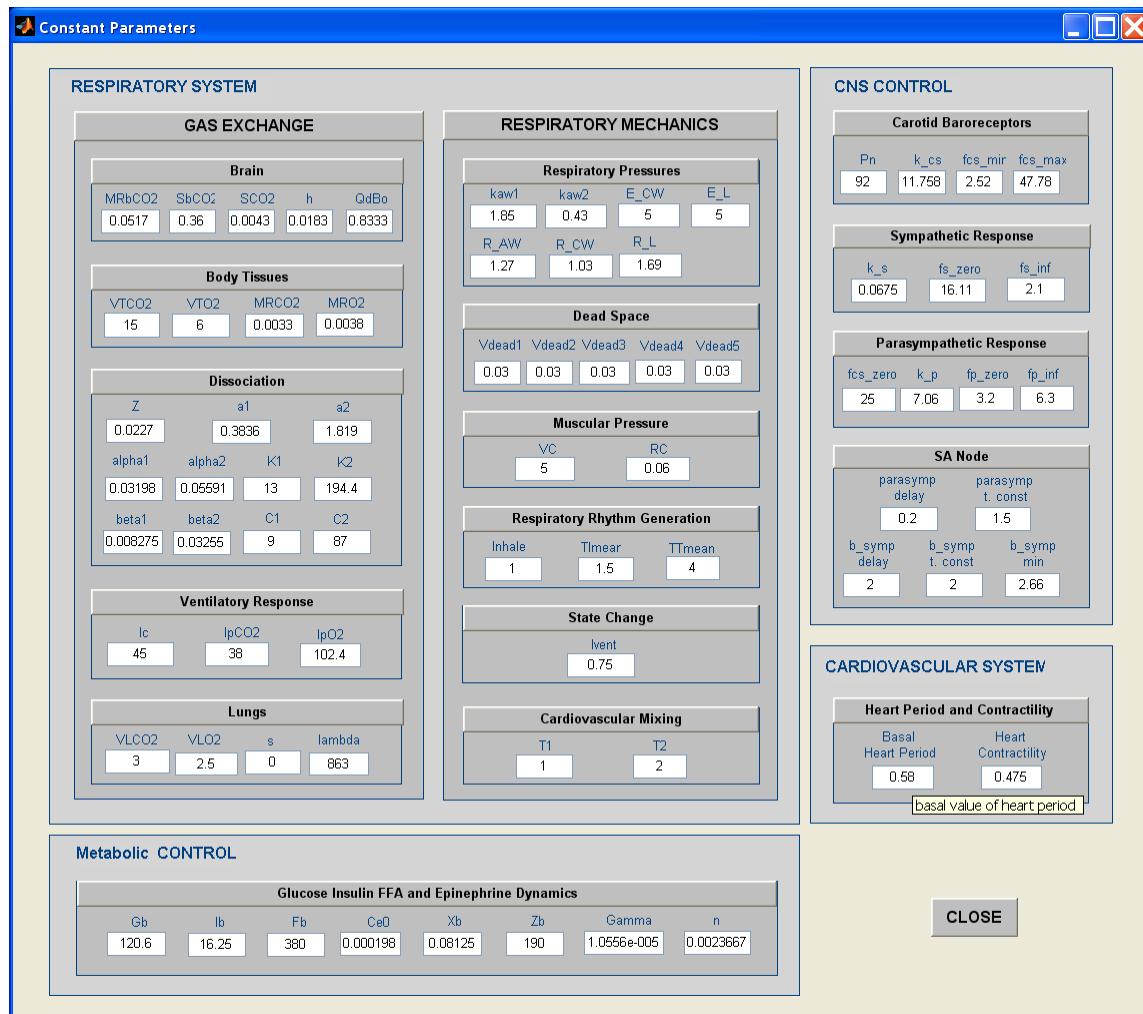
Under “**Open**” menu, the user has three options. “**Open Pneuma Model Ctrl+O**” will show the Pneuma model in Simulink. User can explore the modules in Pneuma and incorporate other blocks if needed. “**Open Display Panel Ctrl+D**” allows the user to see the output from some of the more common measurements such as arterial blood pressure, heart rate and so on. Having achieved some familiarity with PNEUMA, the user may want to add more inputs to the display panel or create new displays. “**Open Program Status Ctrl+P**” will show the Pneuma Progress module in Simulink, that displays the total duration of simulation, current simulation time and percentage of simulation completed, based on total duration of simulation and current simulation time.

If the user wants to load or save the simulation workspace, click under “**File**” menu and two selections will show up. “**Load Data Ctrl+L**” opens the standard Matlab open file window, which allows the user to specify the data file and load the data into workspace. “**Save Data Ctrl+S**” opens the standard Matlab save file window, which allows saving the workspace data to the directory of user's choice.

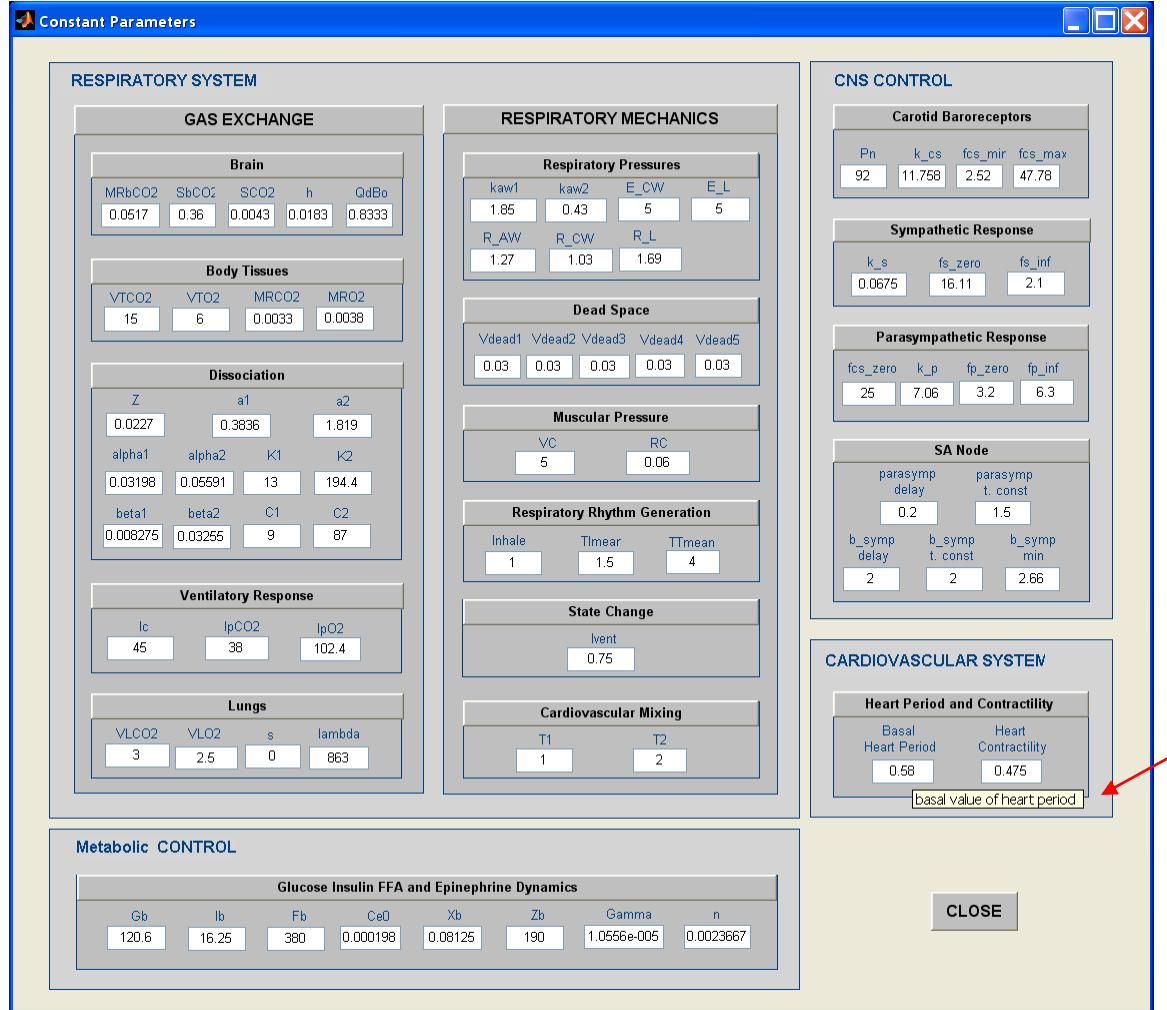
Constant Parameters

When the user clicks on “**CONSTANT PARAMETERS**” button, another graphical interface will appear, as shown below:

These are the constant parameters used in the model. The values may be changed before the simulation, if desired. It is recommended that these parameters be left at their default values. Each model subsystem is listed along with the constant parameter in that compartment. Each title button gives user the opportunity to open the Simulink implementation of that particular subsystem.

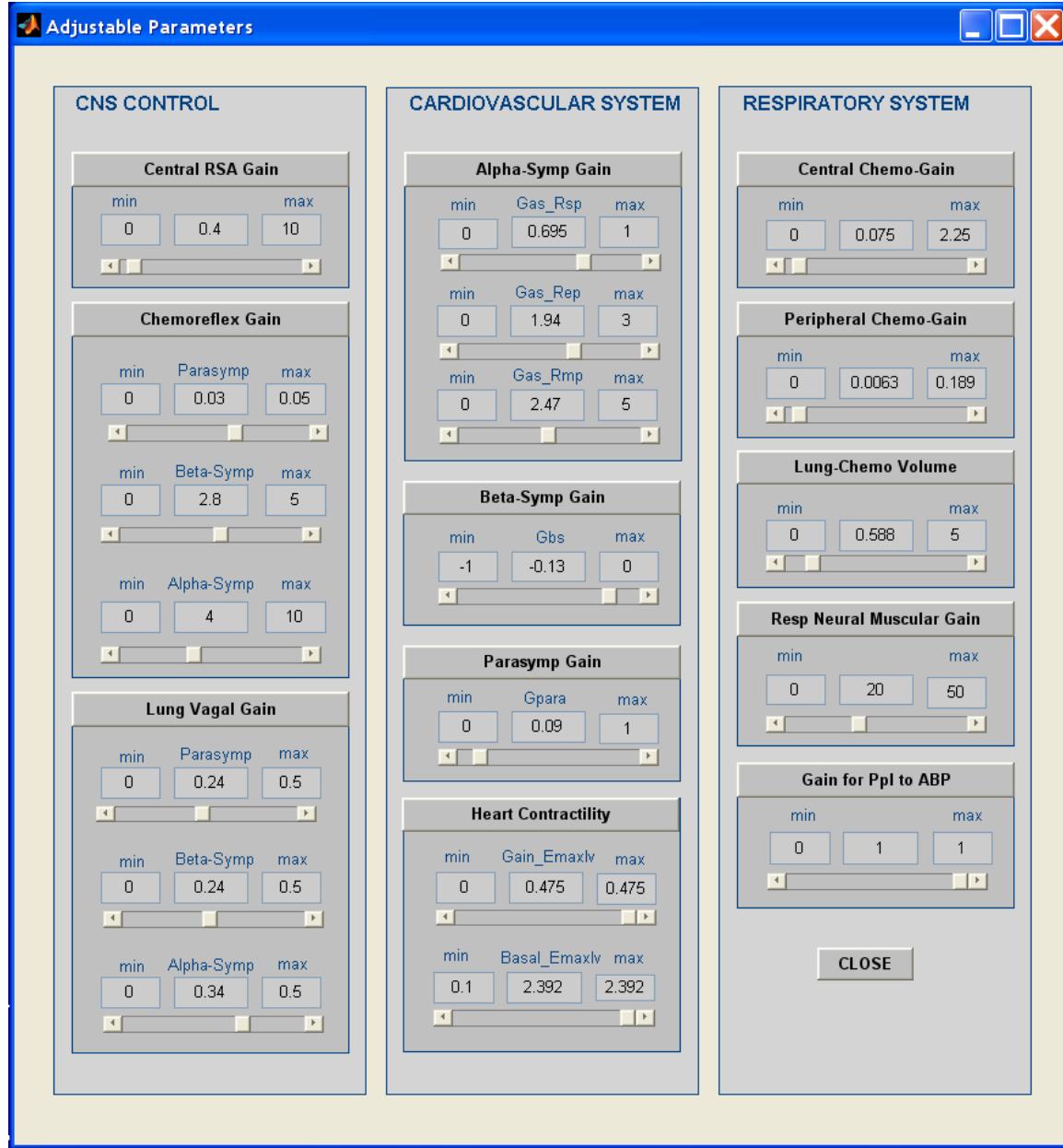


If the mouse cursor is placed and held at a particular box with number, the help text for the corresponding parameter will appear so that the user will know what physiological entity that parameter represents, as shown below:



Adjustable Parameters

This panel allows the user to vary parameters before or during the simulation. Click on “ADJUSTABLE PARAMETERS” button and the following panel will appear:

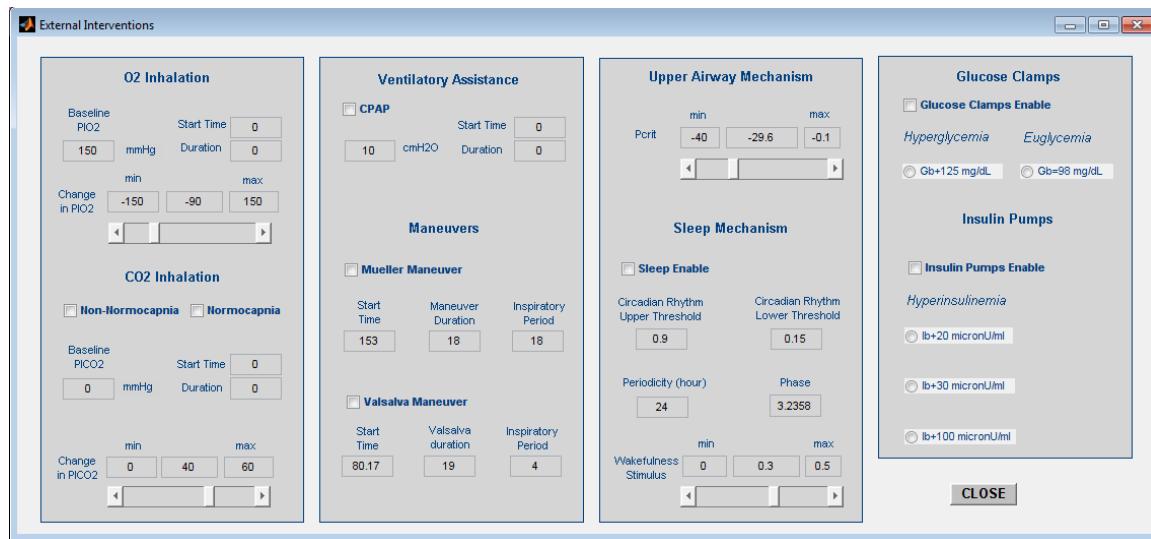


The user can adjust the value either by using the slider bar or by typing directly into the box. Both the “min” and the “max” values are shown for each slider bar. These values can be changed as well. But the values that fall within the default spans indicated are recommended, since these are consistent with physiologically feasible ranges.

The above panel shows the parameters that may be altered in value while the simulation is being executed. Since the model is continually being revised, the actual parameters that can be adjusted may be different in different versions of the program.

External Interventions

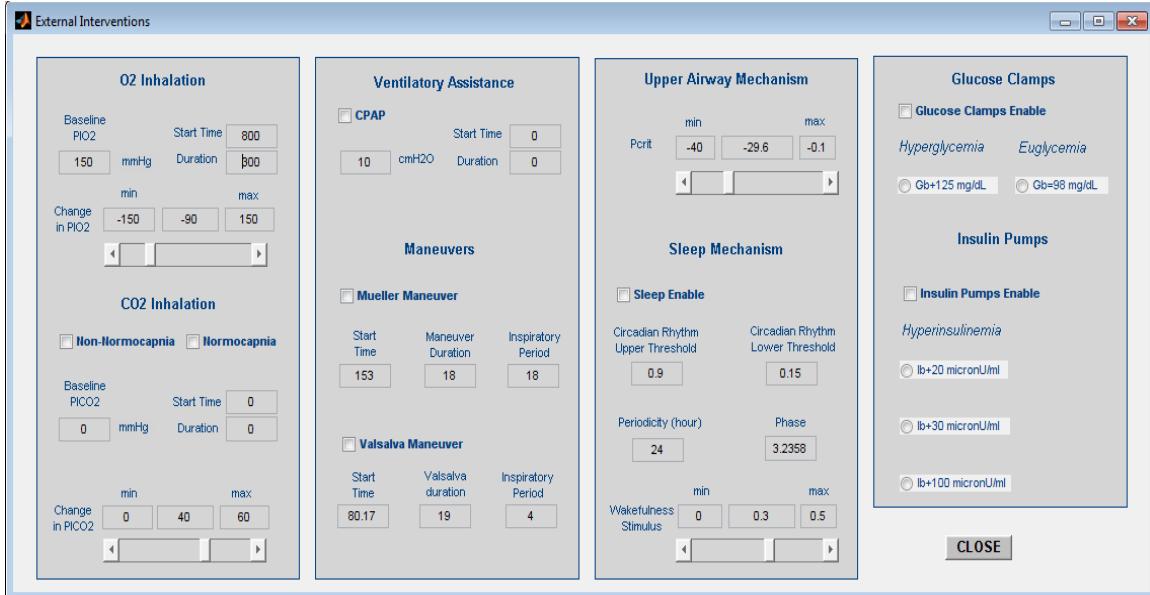
Here, the user is permitted to apply a variety of external interventions to the model. Click on “**EXTERNAL INTERVENTIONS**” and the graphical panel opens up, shown below:



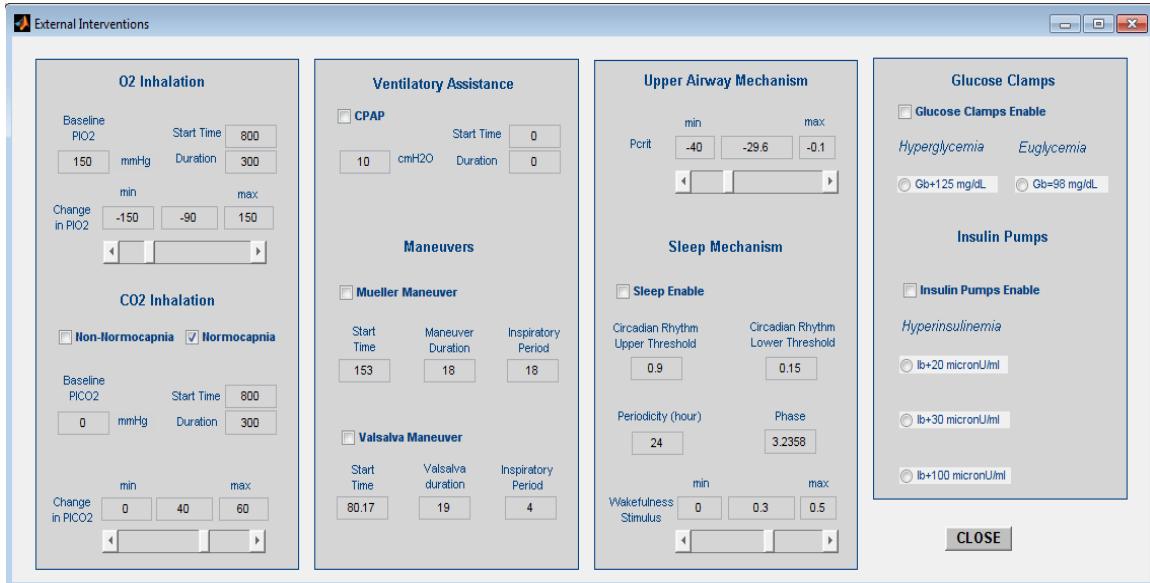
The panel shows the interventions that have been included in the model at the present time. Before you run each intervention, please click “Reset” button on “Control Panel” to reload the original parameter set, then enter your new start/stop time and other parameters on the Control Panel, then go back to the External Interventions. Again, as this software gets updated, other interventions will be added.

The followings are some typical examples for the interventions.

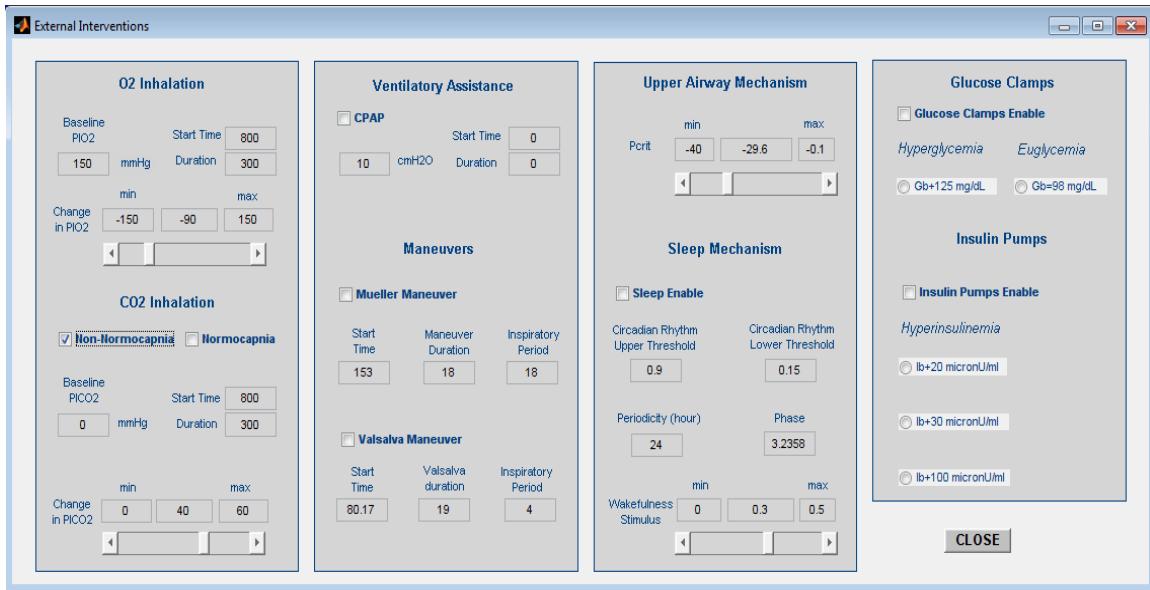
- A. Hypoxia. To simulate hypoxia, simply enter values into “Start Time” and “Duration Time” such as start at 800 sec with duration 300 sec, then enter value into “Change in PIO2” such as “-90” by default, then go back to Control Panel and click on “Run” button, make sure the simulation “End Time” is equal or longer than the hypoxia end time, shown below:



- B. Normocapnic Hypoxia. To simulate normocapnia in hypoxia, first click on check box of “Normocapnia”, then define the hypoxia condition as in Hypoxia, then give the same “Start Time” and “Duration” in CO2 Inhalation part as O2 Inhalation part, then go back to Control Panel and click on “Run” button, shown below:



- C. Non-Normocapnic Hypoxia. To simulate non-normocapnic including hypercapnic hypoxia, first click on check box of “Non-Normocapnia”, then define the hypoxia condition as in Hypoxia, then give the same “Start Time” and “Duration” in CO2 Inhalation part as O2 Inhalation part, then enter value into “Change in PICO2” such as “40” by default, then go back to Control Panel and click on “Run” button, make sure the simulation “End Time” is equal or longer than the hypercapnia end time, shown below:

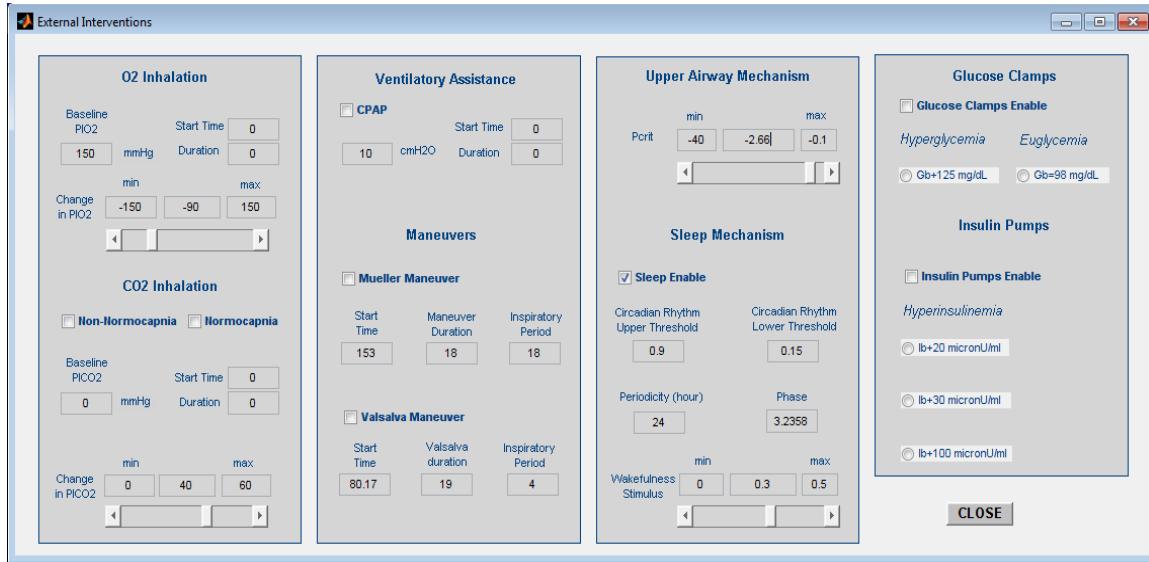


- D. Normal Sleep.** To simulate normal sleep, simply click on check box “Sleep Enable”, then go back to Control Panel and click on “Run” button. You can change the parameter set for sleep to simulation different interventions. For overnight sleep, make sure your “End Time” in Control Panel is longer than $3600*8+200$ seconds (>8 hrs), shown below:

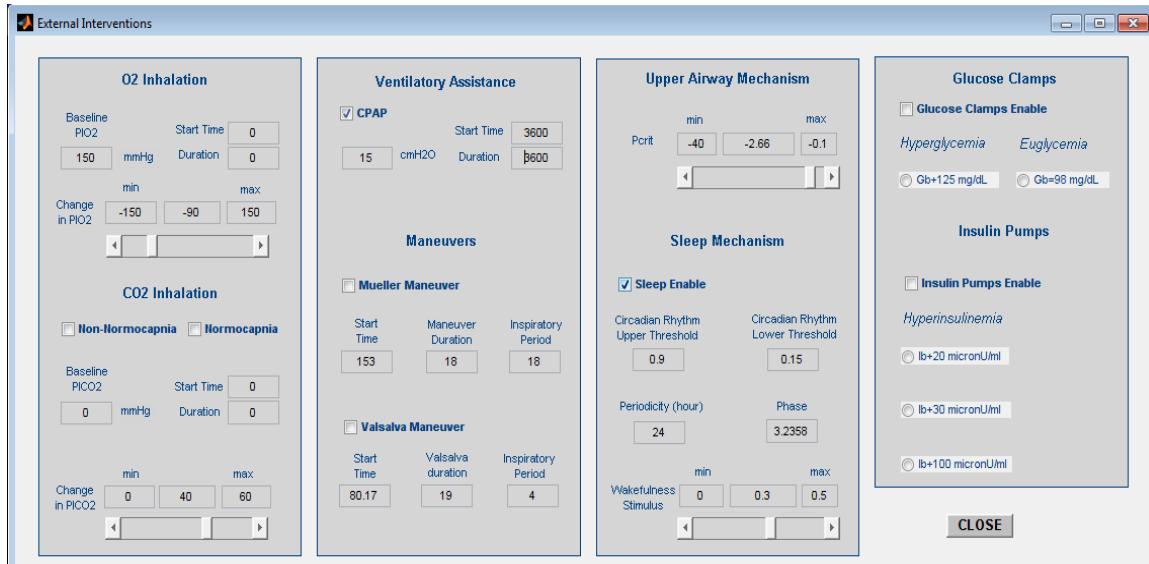


- E. OSA Sleep.** To simulate obstructive sleep apnea (OSA) sleep, first click on check box “Sleep Enable”, then drag the slider button in “Upper Airway Mechanism” or directly enter value into “Pcrit” such as -2.66 which will simulate a moderate OSA, then go back to Control Panel and click on “Run” button. For overnight sleep, make sure your

“End Time” in Control Panel is longer than $3600*9+200$ seconds (>9 hrs) , shown below:



F. CPAP with OSA Sleep. To simulate continuous positive airway pressure (CPAP), first set up OSA sleep as the above example in OSA Sleep. Then click on check box “CPAP”, enter values into “Start Time” and “Duration”, give values for the positive pressure such as 15 cmH₂O, then go back to Control Panel and click on “Run” button. You can try 1 hour CPAP shown as below or overnight CPAP for OSA Sleep. In our model, the default mode is to repeat CPAP every night if the CPAP duration is longer than 1 day. For example, if the simulation runs for 30-day OSA sleep with 10-day CPAP, on in the middle of the 30-day run time simulation, then the CPAP “Start Time” could be $3600*24*10-1800$ sec (which is 0.5 hour short than 10 days) and “Duration Time” could be $3600*24*10+3600*2$ sec (which is 2 hours longer than 10 days).

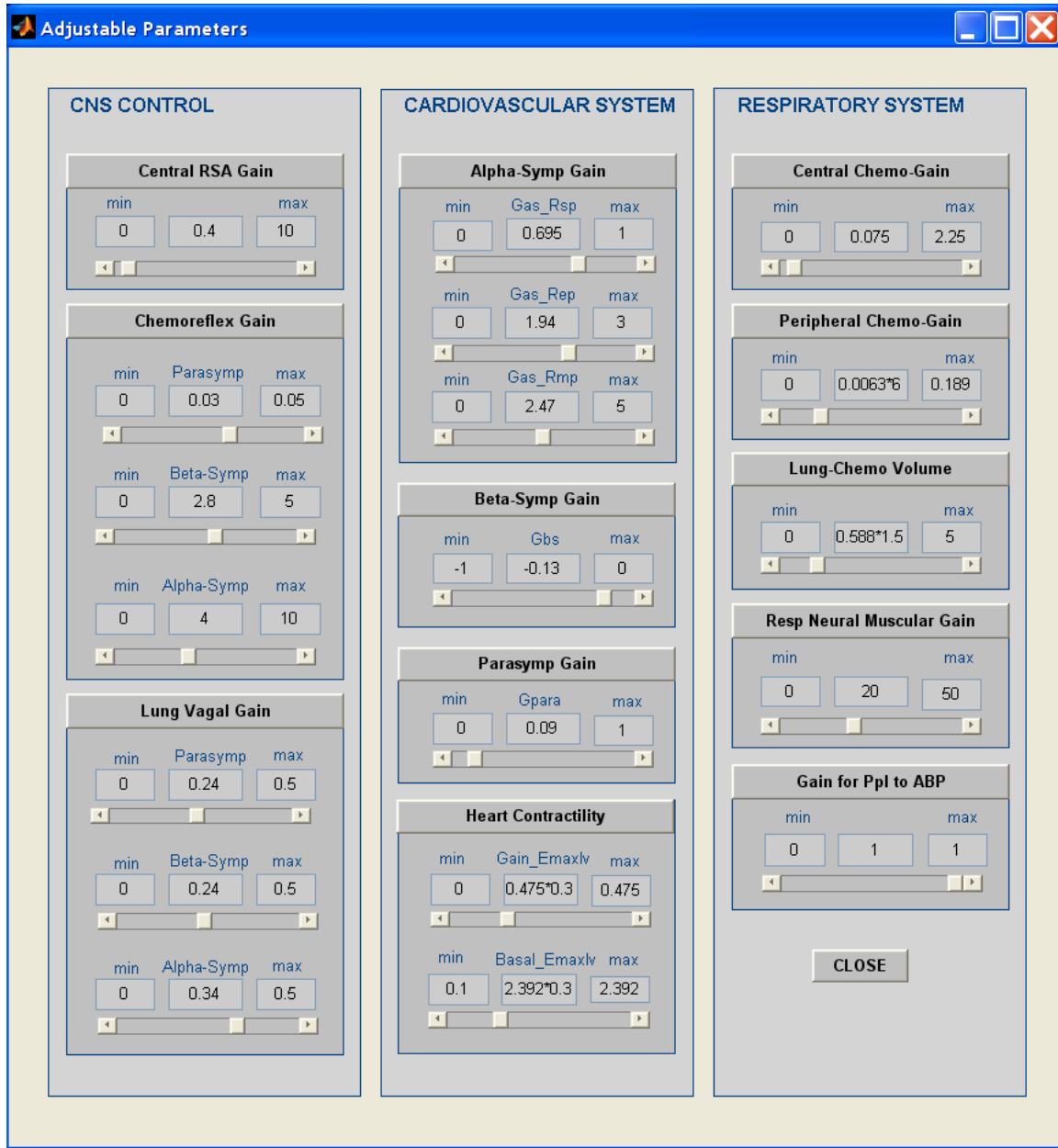


- G. **Maneuvers.** To simulate Mueller Maneuver, click on check box “Mueller Maneuver”, then use the default setup which can be entered with different values as you desire, then go back to Control Panel and click on “Run” button. To simulate Valsalva Maneuver, click on check box “Valsalva Maneuver”, then use the default setup which can be entered with different values as you desired, then go back to Control Panel and click on “Run” button, shown below:



- H. **CSR-CHF Sleep.** To simulate central sleep apnea (CSA characterized with Cheney-Stokes Respiration CSR) with congestive heart failure (CHF), first activate Sleep as in Normal Sleep. Then to change heart contractility, go to “Adjustable Parameters”, enter value such as “ $0.475*0.3$ ” or drag the slider bar for

"Gain_Emaxlv" and enter value such as "2392*0.3" or drag the slider bar for "Basal_Emaxlv" in "Heart Contractility" area, then increase chemoreflex gain such as increase "Peripheral Chemo-Gain" by directly entering value as "0.0063*6" (example value) or dragging the slider bar, then increase "Lung-Chemo Volume" by directly entering value as "0.588*1.5" (example value) or dragging the slider bar. Lastly, go back to Control Panel and click on the "Run" button, as shown below:



These are brief descriptions to help the user get started using our package. Please feel free to explore the model. Since this is an open source environment, contribution of newer code or model will also help us to improve our implementation and to better suit the needs of other users as well.

Block Description

For the complete descriptions of all the individual Simulink model blocks, please refer to the “Blocks Reference” section.

Contact and Support

The whole model and its modularized components will be updated from time to time. So, please check the website for newer update or if you wish to join the mailing list, notification will be sent to you regarding our progress on the update.

FAQ will be set up as we get more questions and comments. In the meantime, please send all your valuable comments and feedbacks to pneuma.bmsr@gmail.com. Once we have the solution, then we will post it in the forum so that other users can benefit from it. The PNEUMA project is supported by the USC Biomedical Simulations Resource (NIH Grant P41-EB001978). Comments and feedback on all aspects of this software are welcome.

Blocks Reference

PNEUMA V.3.0

Description

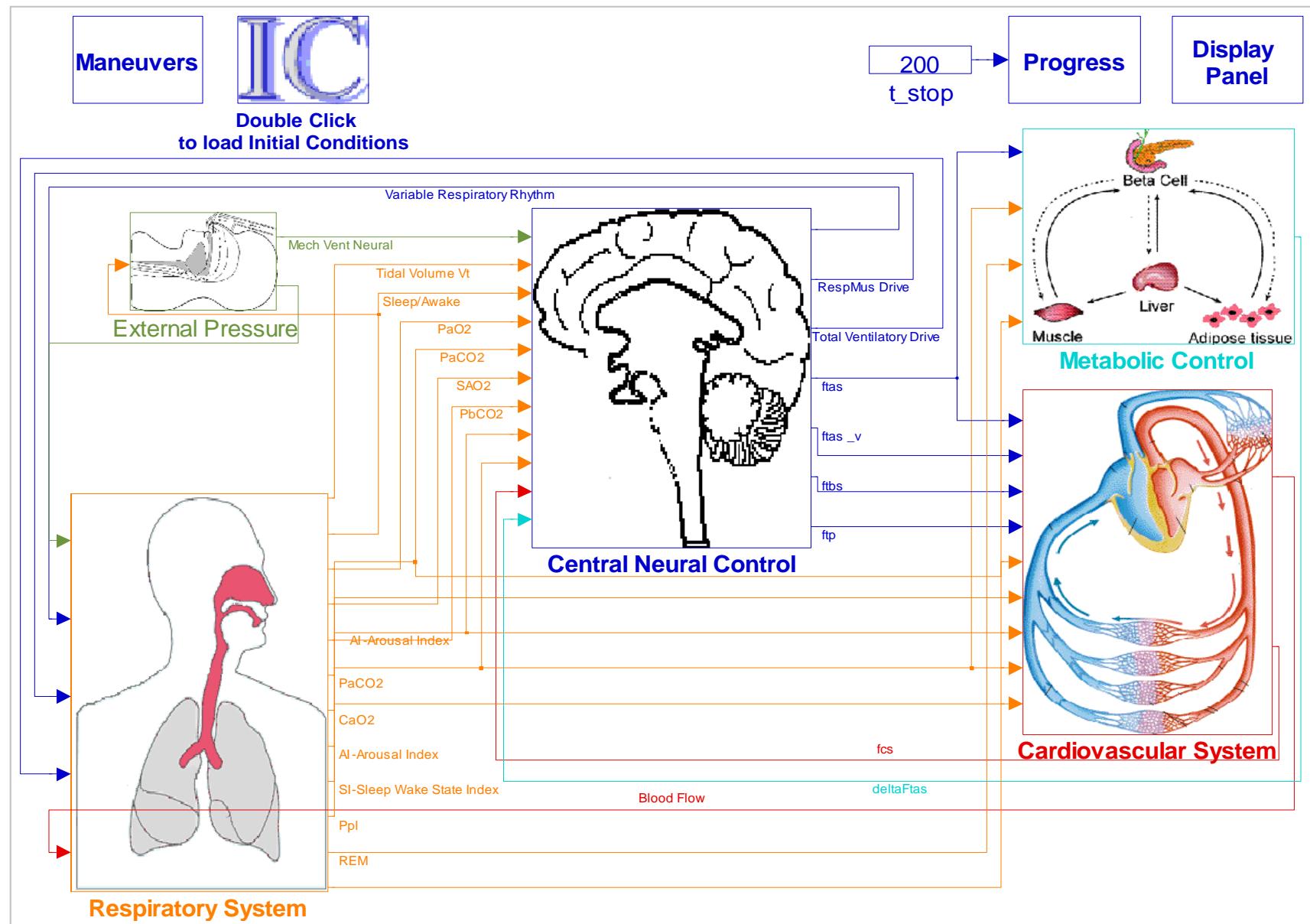
PNEUMA is implemented using SIMULINK. The open architecture of PNEUMA allows to group models into hierarchies to create a simplified view of components or subsystems. High-level information is presented clearly and concisely, while detailed information is easily hidden in subsystems within the model hierarchy. Current PNEUMA implementation builds up on 557 model parameters and allows the tracing of 93 model states. It is a hybrid model that simultaneously addresses fast and slow physiological processes (i.e. single heart beat and circadian rhythm) that are implemented in mixed discrete and continuous modes.

The modular design of PNEUMA makes it possible to perform simulations in which specific physiological mechanisms are excluded or added in order to better determine their contribution to the closed-loop operation of the overall system of interconnected components. This allows the user to explore alternative models of physiologic function *in silico*, which could be very useful in circumventing the challenges of attempting to study the systems in question experimentally or clinically. As well, the modularity of PNEUMA enables users to replace one or more of the model blocks with their own modules of specific physiological components.

General References:

1. Cheng, L., and Khoo, M. C. K. Modeling the autonomic and metabolic effects of obstructive sleep apnea: a simulation study. *Front Physiol* 2:111, 2012. doi: 10.3389/fphys.2011.00111.
2. Cheng, L., Ivanova, O., Fan, H., and Khoo, M. C. K. An integrative model of respiratory and cardiovascular control in sleep-disordered breathing. *Respiratory Physiology and Neurobiology* 174, 4-28, 2010.

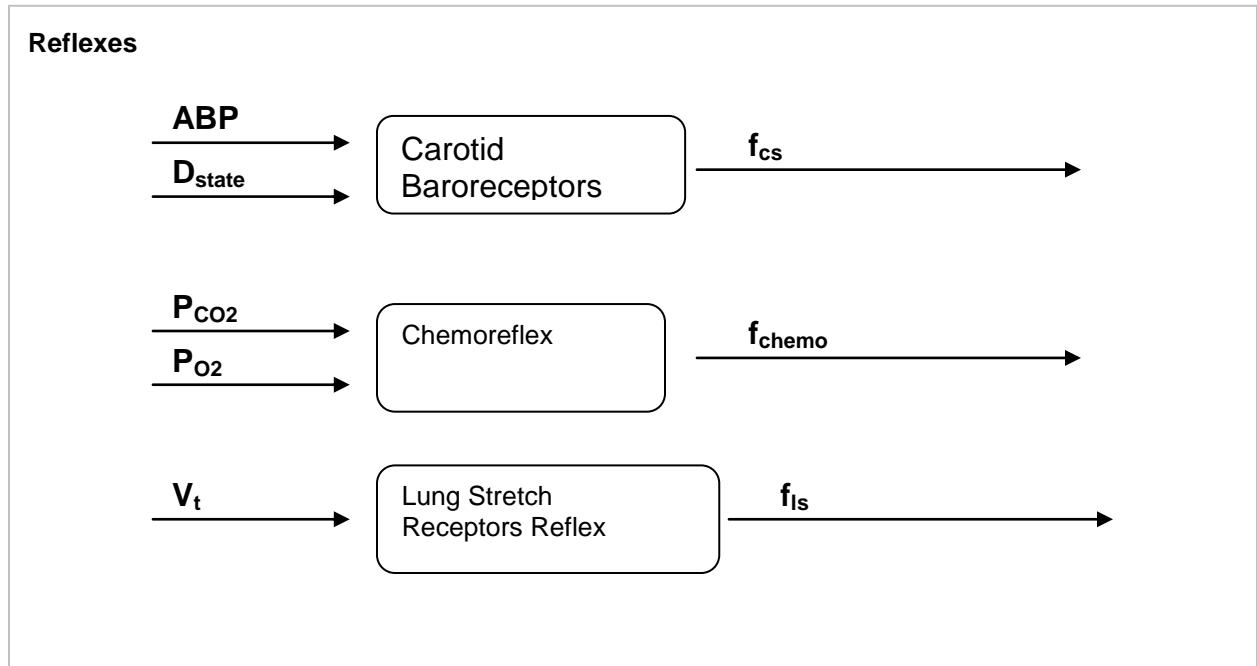
Simulink Model. Overall Pneuma



Reflexes (Reflex_Ursino.mdl)

Description

The reflexes model includes the key cardiorespiratory reflexes: baroreflex, chemoreflex and lung stretch receptor influences on respiration and heart-rate control.



Carotid Baroreceptors

This block represents the pressor receptors that are located in the carotid sinus. In response to arterial blood pressure changes, it produces both parasympathetic and the sympathetic neural activity changes. During sleep, baro-sensitivity is assumed to increase slightly. The input for this compartment is the arterial blood pressure, ABP, and the output is the carotid sinus firing frequency, fcs.

Carotid Baroreceptors Equation:

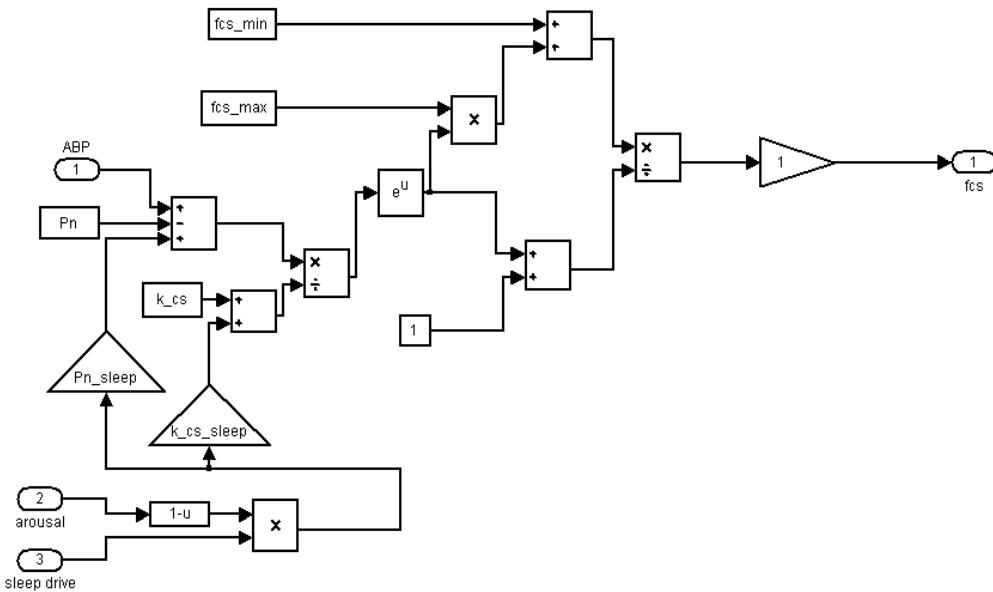
$$f_{cs} = \frac{\left[f_{cs,min} + f_{cs,max} \exp\left(\frac{P - P_n + \theta_{Pn}}{k_{cs} + \theta_{kcs}}\right) \right]}{\left[1 + \exp\left(\frac{P - P_n + \theta_{Pn}}{k_{cs} + \theta_{kcs}}\right) \right]}$$

$$\theta_{Pn} = P_{n_sleep} \cdot (1 - AI) \cdot SI$$

$$\theta_{kcs} = K_{cs_sleep} \cdot (1 - AI) \cdot SI$$

Reference: Ursino, M, Interaction between carotid baroregulation and the pulsating heart: a mathematical model. *American Journal of Physiology*, 275:H1733-H1747, 1998.

Simulink Model: Baroreceptors



Input:	ABP	Arterial Blood Pressure
Output:	f_{cs}	Carotid Sinus firing frequency
Variables:	P_n	Center pressure for sigmoidal function
	k_{cs}	Parameter for sigmoidal slope control
	f_{cs,min}	Lower threshold for sigmoidal function
	f_{cs,max}	Upper saturation for sigmoidal function
	θ_{Pn}	Pressure change in sleep
	θ_{kcs}	Slope change in sleep

Chemoreflex

Description

The inputs to the chemoreflexes are Oxygen (O₂) and Carbon Dioxide (CO₂) levels in the arterial blood. This reflex affects both the heart rate and the peripheral vasculatures. Inputs for this block are the oxygen and carbon dioxide partial pressure, **PaO₂** and **PaCO₂**. Output is the chemoreceptors firing, **fac**.

Chemoreflex Equations:

$$\varphi_{chemo}(Pa_{O_2}, Pa_{CO_2}) = \frac{f_{chemo,min} + f_{chemo,max} \exp\left(\frac{Pa_{O_2} - \bar{Pa}_{O_2}}{k_{chemo}}\right)}{1 + \exp\left(\frac{Pa_{O_2} - \bar{Pa}_{O_2}}{k_{chemo}}\right)} \cdot \left[K \cdot \ln\left(\frac{Pa_{CO_2}}{\bar{Pa}_{CO_2}}\right) + f \right]$$

where

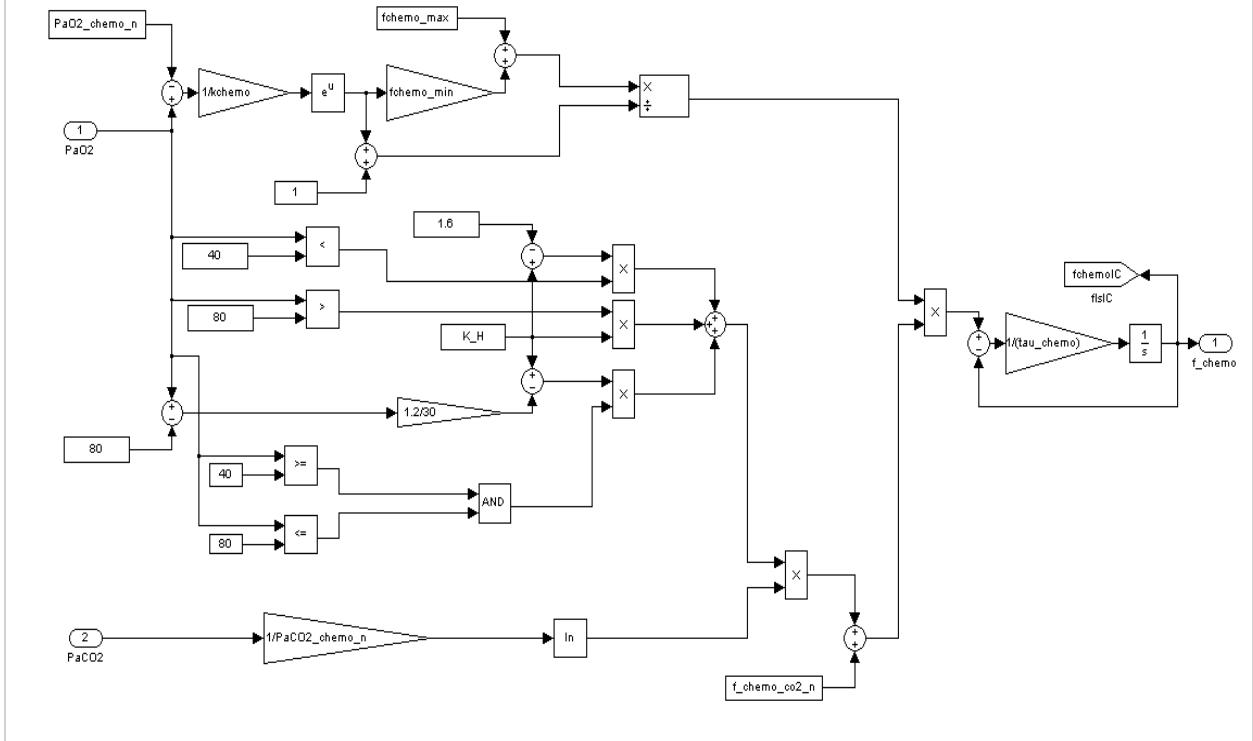
$$K = \begin{cases} K_H & \text{if } Pa_{O_2} > 80 \\ K_H - 1.2 \left(\frac{Pa_{O_2} - 80}{30} \right) & \text{if } 40 \leq Pa_{O_2} \leq 80 \\ K_H - 1.6 & \text{if } Pa_{O_2} < 40 \end{cases}$$

$$\frac{df_{chemo}}{dt} = \frac{1}{\tau_{chemo}} (-f_{chemo} + \varphi_{chemo})$$

Reference: Ursino, M, A mathematical model of CO₂ effect on cardiovascular regulation. *American Journal of Physiology – Heart and Circulatory Physiology*, 281:H2036-H2052, 2001.

Inputs:	PaCO2	Arterial CO2 partial pressure
	PaO2	Arterial O2 partial pressure
Output:	fchemo	Chemoreceptor firing
Variables:	fchemo,max	Lower saturation for the sigmoidal function
	fchemo,min	Upper saturation for the sigmoidal function
	$\overline{PaO_2}$	Center point in the sigmoidal function
	kchemo	Slope control parameter for the sigmoidal function
	$\overline{PaCO_2}$	Normalizing PaCO2 value
	KH	Constant value for the static response
	f	Constant value for the static response
	τchemo	Time constant for the chemoreflex

Simulink Model: Chemoreflex



Lung Stretch Receptor Reflex

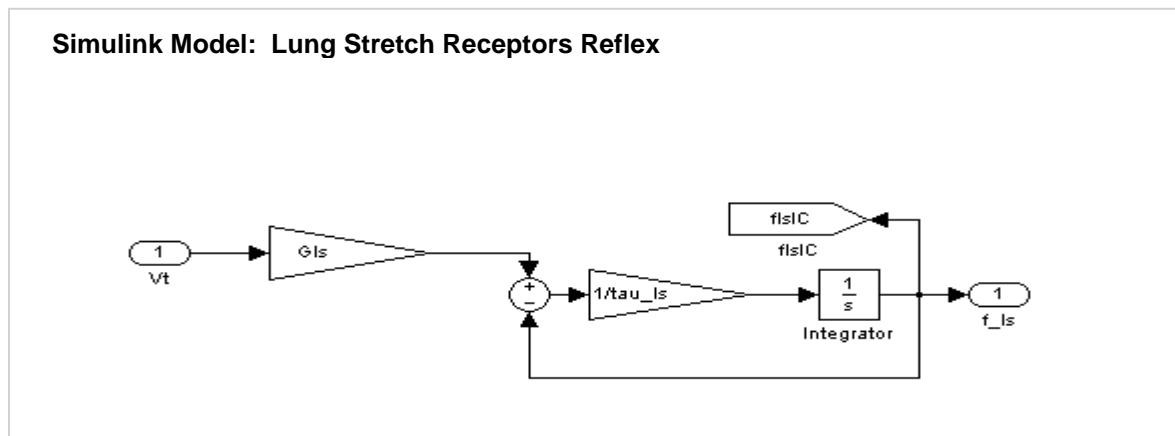
Lung inflation or deflation can produce changes in heart rate through the lung stretch receptors. The input for this block is the tidal volume, V_t . The output is the lung stretch receptor activity, f_{ls} .

Lung Stretch Receptors Reflex Equations

$$\varphi_{lung} = G_{lung} V_T$$

$$\frac{df_{lung}}{dt} = \frac{1}{\tau_{lung}} (-f_{lung} + \varphi_{lung})$$

Reference: Ursino, M, A mathematical model of CO₂ effect on cardiovascular regulation. *American Journal of Physiology – Heart and Circulatory Physiology*, 281:H2036-H2052, 2001.



Inputs:	Vt	Tidal volume
Output:	f_{ls}	Lung stretch receptors firing rate
Variables:	G_{ls}	Constant gain
	T_{ls}	Time constant

Offsets (CNS Response in PNEUMA.mdl)

Offsets for Autonomic Control are the central nervous system response to the partial blood pressure of carbon dioxide and oxygen in the cerebral circulation. The input for this block are partial arterial blood pressure PaCO_2 and PaO_2 . The outputs are the offsets for autonomic control, $\text{Offset}_{\text{res,vein,heart}}$, respectively.

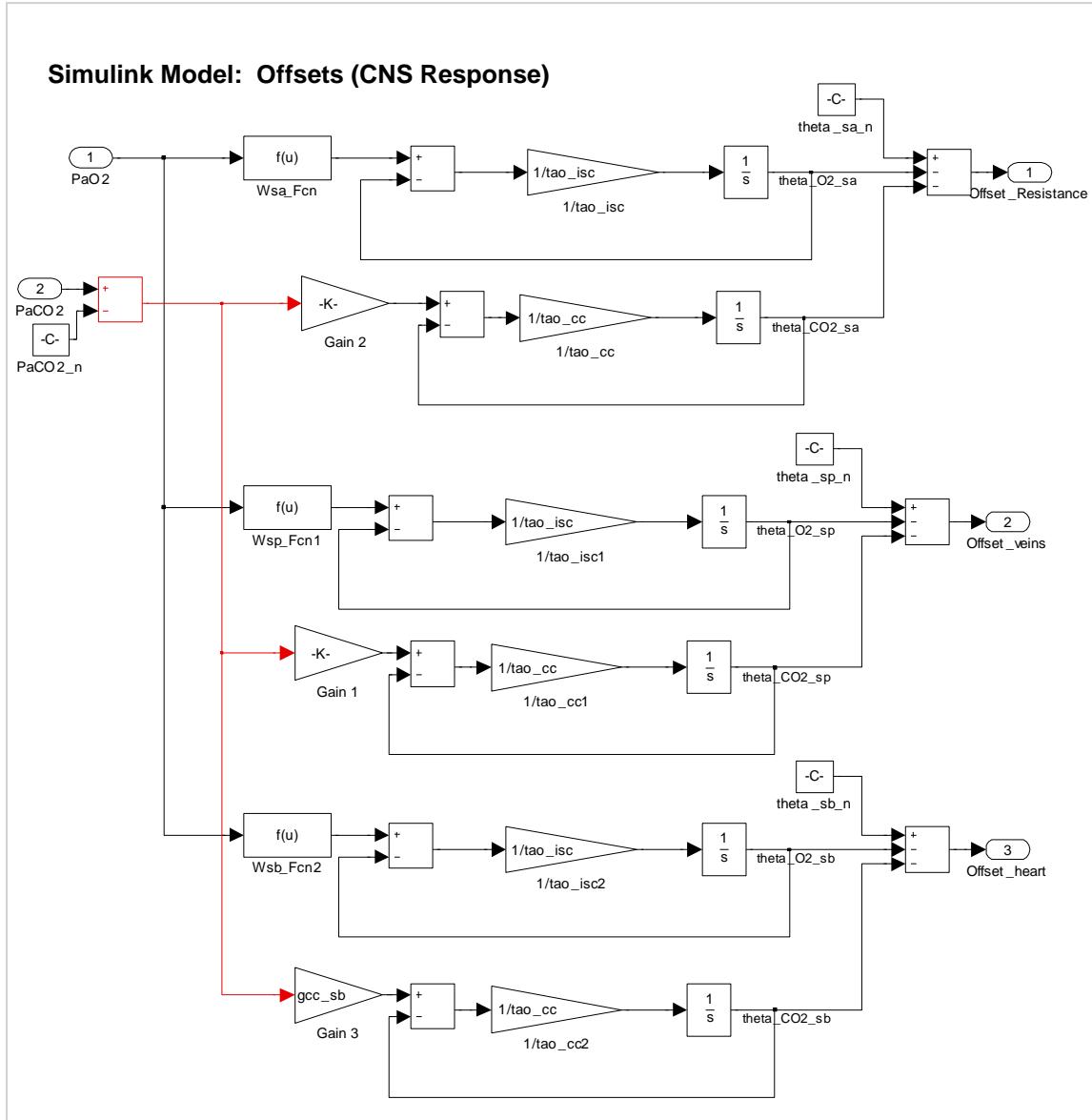
Offsets Equations

$$\begin{aligned} \text{Offset}_{\text{res,vein,heart}} &= \theta_{\text{san,spn,sbn}} - \theta_{\text{O2sa,O2sp,O2sb}} - \theta_{\text{CO2sa,CO2sp,CO2sb}} \\ \frac{d\theta_{\text{O2sa,O2sp,O2sb}}}{dt} &= \frac{1}{\tau_{\text{isc}}} (-\theta_{\text{O2sa,O2sp,O2sb}} + W_{\text{sa,sp,sb}}) \\ \frac{d\theta_{\text{CO2sa,CO2sp,CO2sb}}}{dt} &= \frac{1}{\tau_{\text{cc}}} [-\theta_{\text{CO2sa,CO2sp,CO2sb}} + \text{gcc}_{\text{sa,sp,sb}} \cdot (\text{P}_{\text{aCO}_2} - \text{P}_{\text{aCO2n}})] \\ W_{\text{sa,sp,sb}} &= X_{\text{sa,sp,sb}} / (1 + \exp((\text{P}_{\text{aO}_2} - \text{PO2n}_{\text{sa,sp,sb}}) / \text{kisc}_{\text{sa,sp,sb}})) \end{aligned}$$

Reference: Ursino, M, A mathematical model of CO_2 effect on cardiovascular regulation. *American Journal of Physiology - Heart and Circulatory Physiology*, 281:H2036-H2052, 2001.

Inputs:	PaCO₂	Arterial CO ₂ partial pressure
	PaO₂	Arterial O ₂ partial pressure
Output:	Offset_{res,vein,heart}	CNS Response as offsets of autonomic control
Variables:	X_{sa}	Saturation for the offset of α-sympathetic activity on peripheral resistance
	θ_{san}	Nominal level of offset of α-sympathetic activity on peripheral resistance
	PO2n_{sa}	Central point for the sigmoidal function
	kisc_{sa}	Parameter of α-sympathetic activity on peripheral resistance
	X_{sb}	Saturation for the offset of β-sympathetic activity
	θ_{sbn}	Nominal level of offset of β-sympathetic activity
	PO2n_{sb}	Central point for the sigmoidal function
	kisc_{sb}	Parameter of β-sympathetic activity
	X_{sp}	Saturation for the offset of α-sympathetic activity on peripheral resistance
	θ_{spn}	Nominal level of offset of α-sympathetic

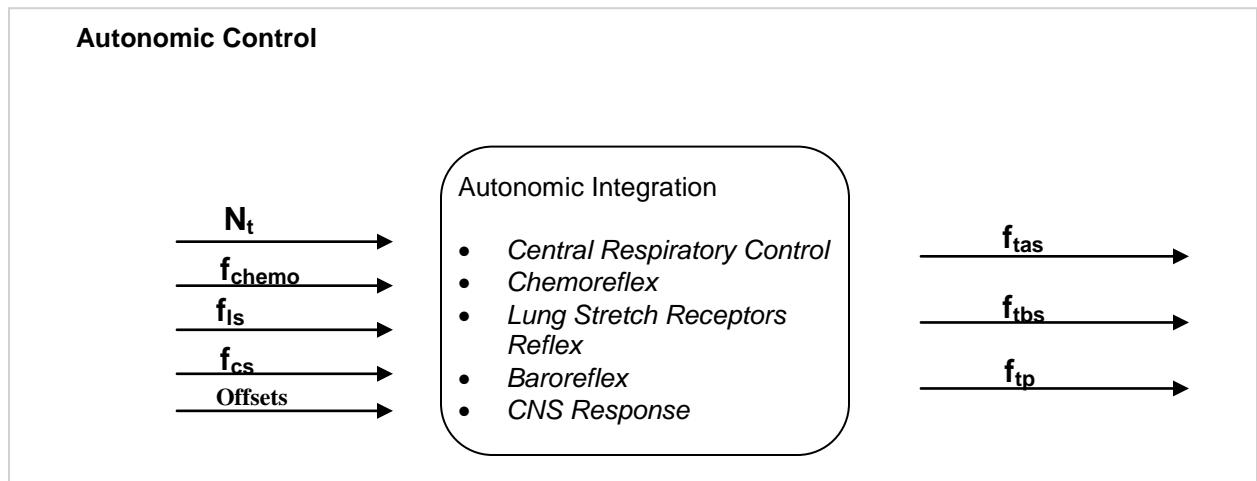
		activity on peripheral resistance
	PO2n_{sp}	Central point for the sigmoidal function
	kisc_{sp}	Parameter of α -sympathetic activity on unstressed volume of veins
	τ_{isc}	Time constant for oxygen response
	τ_{cc}	Time constant for carbon dioxide response



Autonomic Control (submodels refer to Autonomic.mdl)

Description

Influences from the central respiratory control (RSA), baroreflexes, chemoreflexes and lung stretch receptors reflexes are integrated in this compartment and these inputs determine the total α -sympathetic, β -sympathetic and parasympathetic influences on heart rate and peripheral resistance. The inputs for this compartment are the central respiratory drive, N_t , chemoreflex, f_{chemo} , lung stretch receptors reflex, f_{ls} , carotid baroreceptors firing, f_{cs} , and CNS response, **Offsets**. The outputs are the α -sympathetic response, f_{tas} , β -sympathetic response, f_{tbs} and parasympathetic response, f_{tp} . The models shown below is in PNEUMA.mdl, but the submodel is referred to Autonomic.mdl.



Autonomic Integration Equations:

(a) Alpha-Sympathetic Activity

$$f_{tas_res,vein} = f_{s,\infty} + (f_{s,0} - f_{s,\infty}) \cdot \exp \left[k_s \cdot \left(-G_{baro,as} f_{cs} + G_{chemo,as} f_{chemo} - G_{lung,as} f_{lung} - G_{RSA,as} N_t - Offset_{res,vein} \right) \right]$$

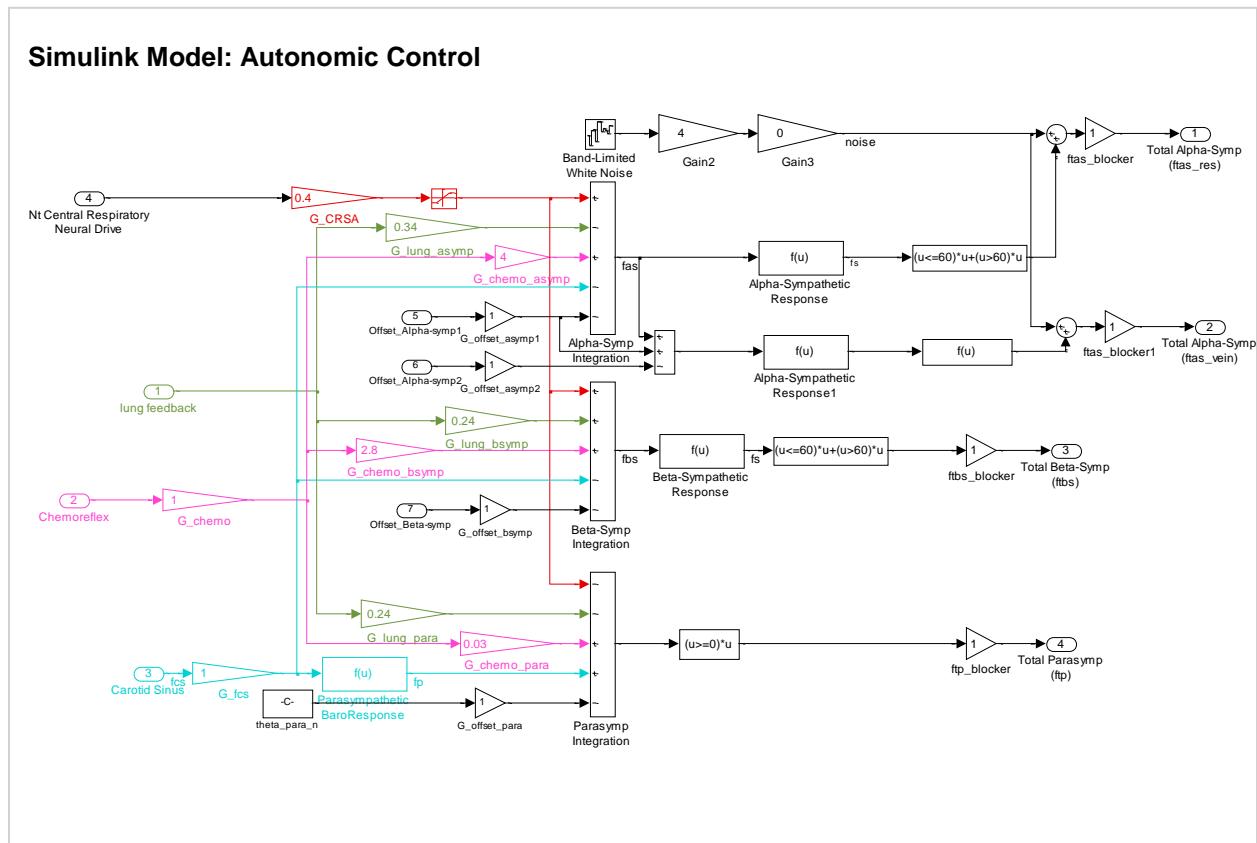
(b) Beta-Sympathetic Activity

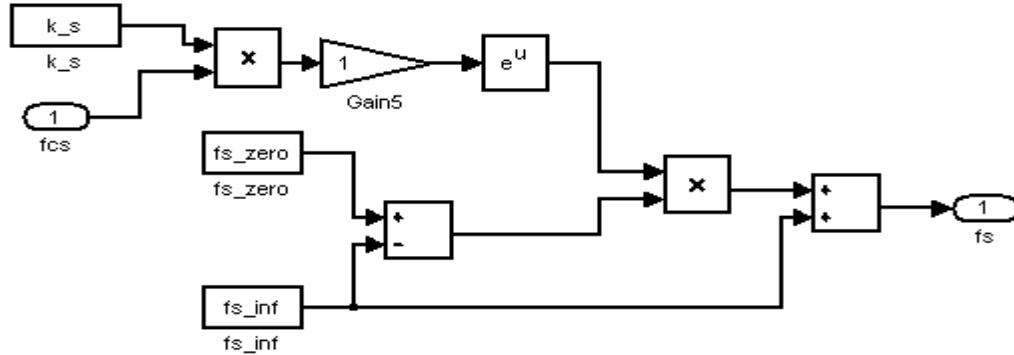
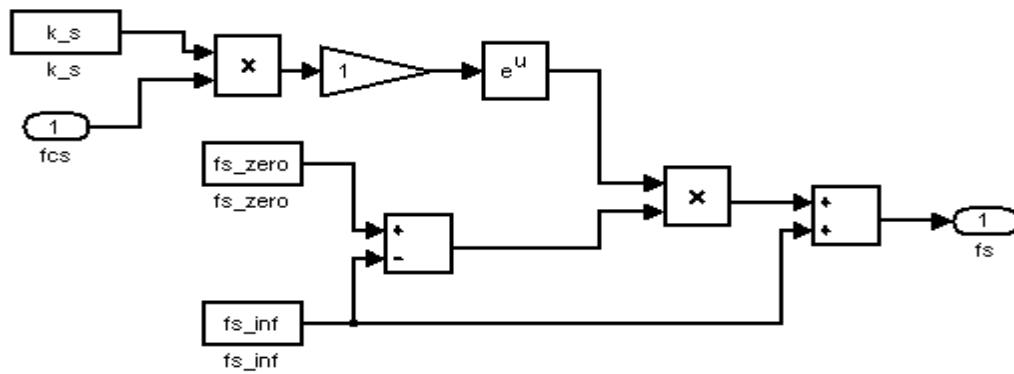
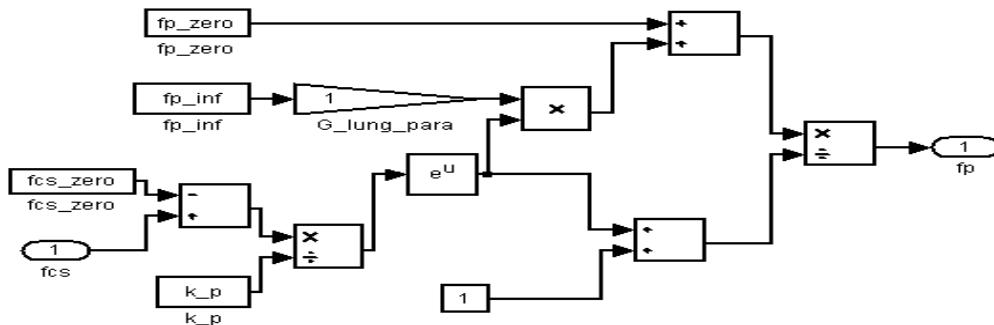
$$f_{tbs} = f_{s,\infty} + (f_{s,0} - f_{s,\infty}) \cdot \exp \left[k_s \cdot \left(-G_{baro,bs} f_{cs} + G_{chemo,bs} f_{chemo} + G_{lung,bs} f_{lung} + G_{RSA,bs} N_t - Offset_{heart} \right) \right]$$

(c) Parasympathetic Activity

$$f_{tp} = \frac{\left[f_{para,0} + f_{para,\infty} \cdot \exp\left(\frac{f_{cs} - f_{cs,0}}{k_p}\right) \right]}{\left[1 + \exp\left(\frac{f_{cs} - f_{cs,0}}{k_p}\right) \right]} + G_{chemo,p} f_{chemo} + G_{lung,p} f_{lung} - G_{RSA,p} N_t - Offset_{para_n}$$

Reference: Ursino, M, A mathematical model of CO₂ effect on cardiovascular regulation. *American Journal of Physiology – Heart and Circulatory Physiology*, 281:H2036-H2052, 2001.



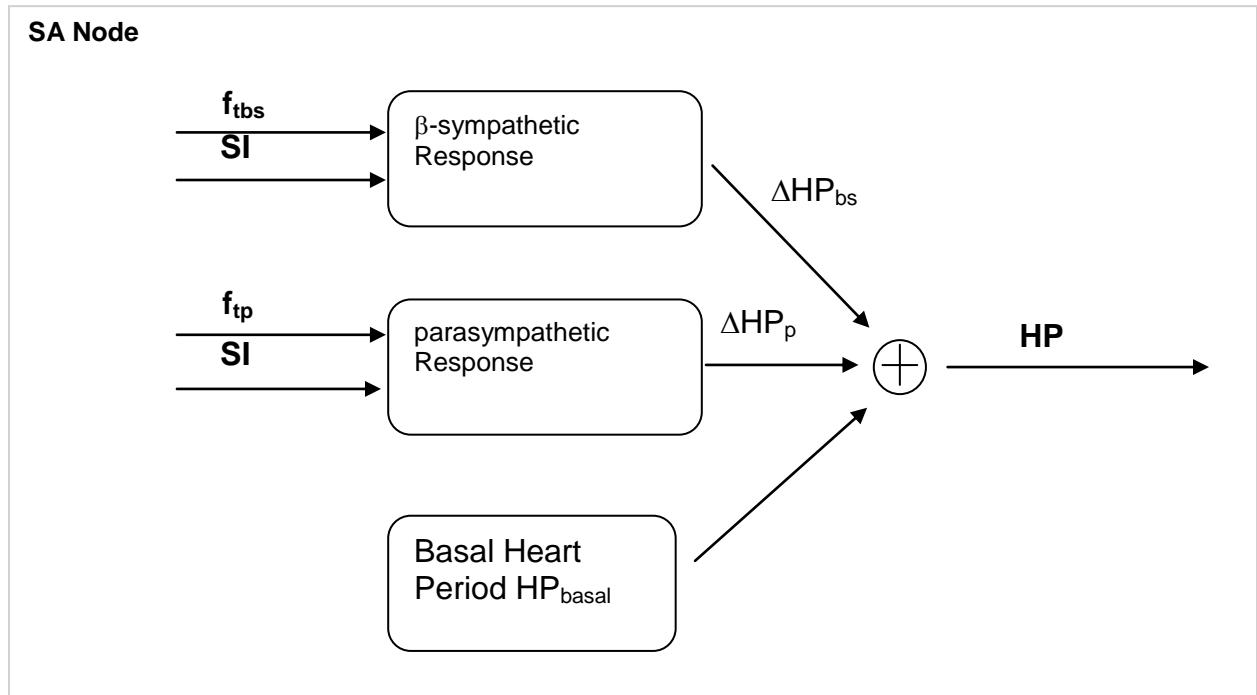
Simulink Model: Alpha-Sympathetic Response**Simulink Model: Beta-Sympathetic Response****Simulink Model: Parasympathetic Baroresponse**

Inputs:	N_t	Respiratory Neural firings
e	f_{chemo}	Chemoreceptor firings
	f_{lung}	Lung stretch receptors firings
	f_{cs}	Baroreceptor firings
	$Offset_{res,vein,heart}$	CNS response
Outputs:	f_{tp}	Total parasympathetic response
	f_{tbs}	Total β -Sympathetic response
	$f_{tas_res,vein}$	Total α -Sympathetic response
Variables:	$f_{para,0}$	Lower threshold of the parasympathetic baroreflex sigmoidal function
	$f_{para,\infty}$	Upper saturation of the parasympathetic baroreflex sigmoidal function
	$f_{cs,0}$	Center point for the sigmoidal function
	k_p	Slope control parameter for the sigmoidal function
	$G_{RSA,p}$	Central RSA gain for parasympathetic response
	$G_{chemo,p}$	Chemoreflex gain for parasympathetic response
	$G_{lung,p}$	Lung stretch receptor reflex gain for parasympathetic response
	$f_{s,0}$	Lower limit of the sympathetic exponential decay function
	$f_{s,\infty}$	Upper saturation of the sympathetic exponential decay function
	k_s	Constant for the exponential function
	$G_{RSA,bs}$	Central RSA gain for β -sympathetic response
	$G_{chemo,bs}$	Chemoreflex gain for β -sympathetic response
	$G_{lung,bs}$	Lung stretch receptor reflex gain for β -sympathetic
	$G_{baro,bs}$	Baroreflex gain for β -sympathetic
	$G_{RSA,as}$	Central RSA gain for α -sympathetic response
	$G_{chemo,as}$	Chemoreflex gain for α -sympathetic response
	$G_{lung,as}$	Lung stretch receptor reflex gain for α -sympathetic
	$G_{baro,as}$	Baroreflex gain for α -sympathetic

SA Node (SA_Node_Ursino.mdl)

Description

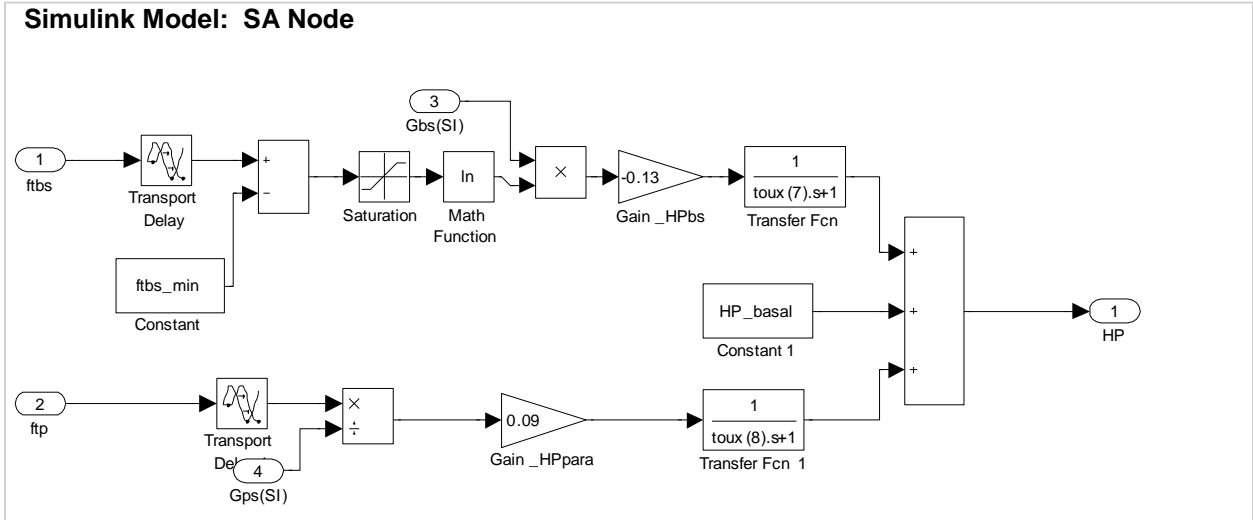
This module translates changes in β -sympathetic and parasympathetic efferent activity into changes in heart rate. In sleep, the model assumes that the parasympathetic response increases while there is small decrease in the sympathetic activity. The inputs for this subsystem are the total β -sympathetic firing frequency, f_{tbs} , and parasympathetic firing frequency, f_{tp} , and the output is the heart period, HP (= reciprocal of instantaneous heart rate).



SA Node Equation:

$$HP = \Delta HP_{bs} + \Delta HP_p + HP_{basal}$$

Reference: Ursino, M, Interaction between carotid baroregulation and the pulsating heart: a mathematical model. *American Journal of Physiology*, 275:H1733-H1747, 1998.



Inputs:	f_{tbs}	Total beta-sympathetic firing frequency
	f_{tp}	Total parasympathetic firing frequency
Output:	HP	Heart Period (equivalent to RR-interval)
Variable:	HP_{basal}	Basal value for HP for denervated heart
	ΔHP_{bs}	Change in HP modulated by β -sympathetic response
	ΔHP_p	Change in HP modulated by parasympathetic response

β -Sympathetic Control

Description

This response is modeled assuming first-order dynamics. The time-constant and delay associated with the β -sympathetic effect on the heart period is longer than that of the parasympathetic response. There is slight decrease in β -sympathetic response in sleep. The input for this compartment is the β -sympathetic firing frequency, ftbs and the output is the corresponding component of heart period change, ΔHP_{bs} .

β -Sympathetic Control Equations:

$$\sigma_{bs}(t) = \begin{cases} G_{bs} \cdot G_{bs}(SI) \cdot \ln[f_{tbs}(t - D_{bs}) - f_{tbs\ min} + 1], & f_{tbs} \geq f_{tbs\ min} \\ 0, & f_{tbs} < f_{tbs\ min} \end{cases}$$

$$G_{bs}(SI) = 1 - SI \cdot (1 - AI) \cdot G_{bs_sleep}$$

$$\frac{d}{dt} \Delta HP_{bs} = \frac{1}{\tau_{bs}} [-\Delta HP_{bs}(t) + \sigma_{bs}(t)]$$

Reference: Ursino, M, Interaction between carotid baroregulation and the pulsating heart: a mathematical model. *American Journal of Physiology*, 275:H1733-H1747, 1998.

Input:	ftbs	Total beta-sympathetic firing frequency
	SI	Sleep Index for sleep wake state
	AI	Arousal Index
Output:	ΔHP_{bs}	Heart Period change modulated by β -symp.
Variables:	D_{bs}	β -sympathetic time delay
	ftbsIC	β -sympathetic initial output after time delay
	ftbs_min	Lower limit for the natural log function
	G_{bs}	β -sympathetic Gain varied with sleep drive
	τ_{bs}	β -sympathetic time constant
	delta_HPbsIC	Initial input to the β -symp first order dynamic system
	G_{bs_sleep}	β -sympathetic Gain of sleep factor

Parasympathetic Response

Description

The vagal effect on heart rate is modeled assuming first-order dynamics. During sleep, parasympathetic activity increases, and this is partially responsible for the decrease in the heart rate. The input for this compartment is the parasympathetic firing frequency, ftp and the output is the corresponding component of heart period change, ΔHP_p .

Parasympathetic Response Equations:

$$\sigma_{ps}(t) = \frac{G_{ps}}{G_{ps}(SI)} \cdot f_{tp}(t - D_{ps})$$

$$\frac{d}{dt} \Delta HP_p = \frac{1}{\tau_{para}} [-\Delta HP_p(t) + \sigma_p(t)]$$

$$G_{ps}(SI) = 1 - SI \cdot (1 - AI) \cdot G_{para_sleep}$$

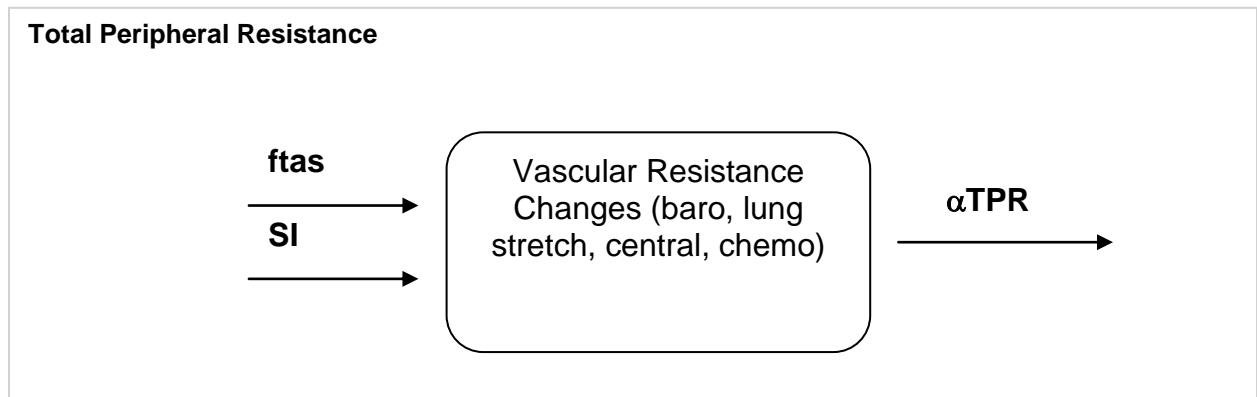
Reference: Ursino, M, Interaction between carotid baroregulation and the pulsating heart: a mathematical model. *American Journal of Physiology*, 275:H1733-H1747, 1998.

Input:	ftp	Total parasympathetic firing frequency
	SI	Sleep Index for sleep wake state
	AI	Arousal Index
Outputs:	ΔHPp	Heart Period change modulated by parasympathetic
Variables:	Dpara	Parasympathetic time delay
	ftpIC	Parasympathetic initial output after time delay
	Gpara	Parasympathetic Gain varied with sleep drive
	τpara	Parasympathetic time constant
	delta_HPpIC	Initial input to the parasympathetic first order dynamic system
	Gpara_sleep	Parasympathetic Gain of sleep factor

α -Sympathetic Control of Peripheral Resistance (TPR_Ursino.mdl)

Description

This block models α -sympathetic control of peripheral vascular resistance, using a first-order dynamic system as in the case of the β -sympathetic component. During sleep in normals, the accompanying decrease in α -sympathetic activity contributes substantially to a decrease in blood pressure. The inputs are the total α -sympathetic firing frequency, ftas and the state/sleep drive, Dstate. The output is the proportional change in the peripheral resistance, α TPR.



Equations for Total Peripheral Resistance Change:

$$Z_j = \begin{cases} G_j \cdot G_{as}(SI) \cdot \ln[f_{tas_i}(t - D_j) - f_{tas\ min} + 1], & f_{tas_i} \geq f_{tas\ min} \\ 0, & f_{tas_i} < f_{tas\ min} \end{cases}$$

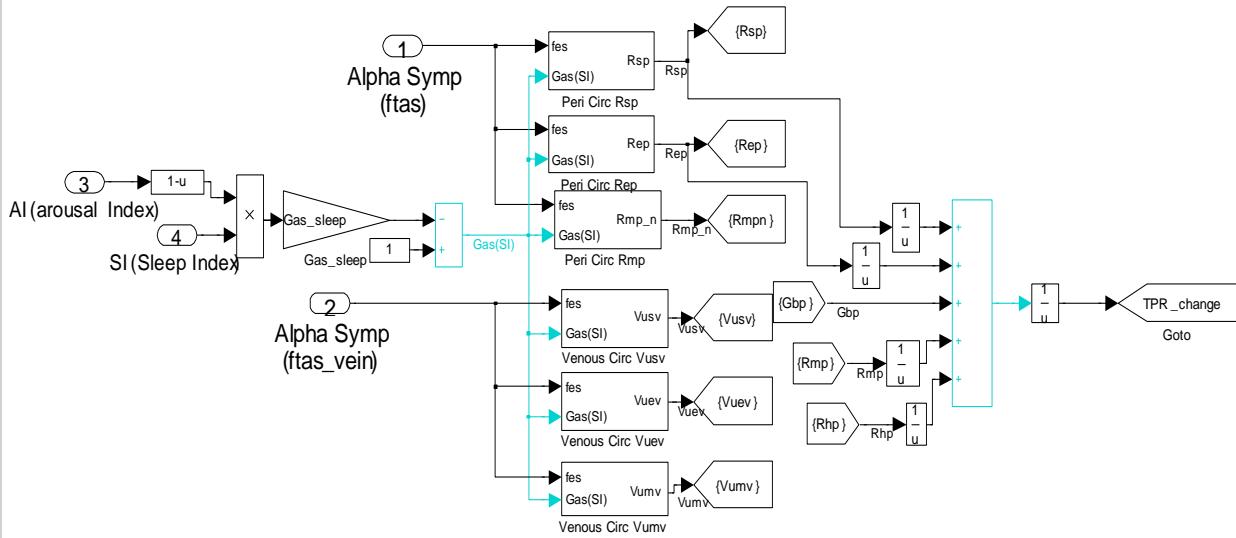
$$\frac{d\Delta TPR_j}{dt} = \frac{1}{\tau_j}(-\Delta TPR_j + Z_j)$$

$$TPR_j(t) = \Delta TPR_j + TPR_{j0}$$

$$G_{as}(SI) = 1 - SI \cdot (1 - AI) \cdot G_{as_sleep}$$

Reference: Ursino, M, Interaction between carotid baroregulation and the pulsating heart: a mathematical model. *American Journal of Physiology*, 275:H1733-H1747, 1998.

Simulink Model: Alpha-Sympathetic Modulation on Peripheral Resistance



Inputs:	ftas	Total alpha-sympathetic firing frequency
	SI	Sleep Index for sleep wake state
	AI	Arousal Index
Outputs:	TPR_change	TPR change factor
Variables:	fasIC	α -sympathetic initial output after time delay
	fas_min	Lower limit for the natural log function
	Gas_sleep	α -sympathetic Gain varied with sleep
	Gas_sp	α -sympathetic Gain for splanchnic peripheral resistance
	tas_sp	α -sympathetic time constant
	Das_sp	Delay α -sympathetic time constant
	Gas_ep	α -sympathetic Gain for extra-splanchnic peripheral resistance
	tas_ep	α -sympathetic time constant
	Das_ep	Delay α -sympathetic time constant
	Gas_mp	α -sympathetic Gain for skeletal muscle peripheral resistance
	tas_mp	α -sympathetic time constant
	Das_mp	Delay α -sympathetic time constant
	Vusv0	Basal level of unstressed volume of splanchnic venous circulation
	Gas_usv	α -sympathetic Gain for unstressed volume of splanchnic venous circulation
	tas_usv	α -sympathetic time constant
	Das_usv	Delay α -sympathetic time constant

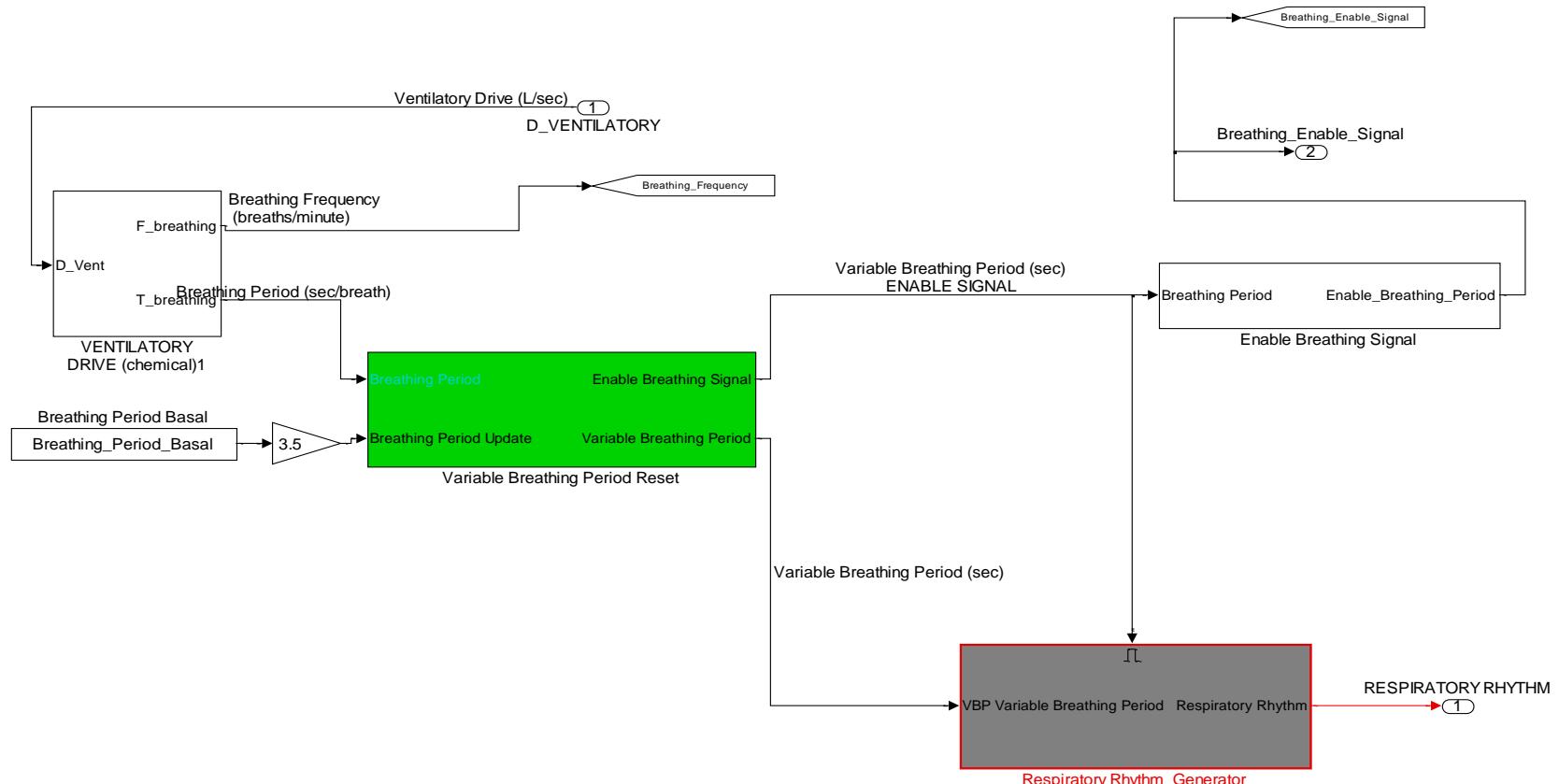
Variable Breathing Period (PNEUMA.mdl)

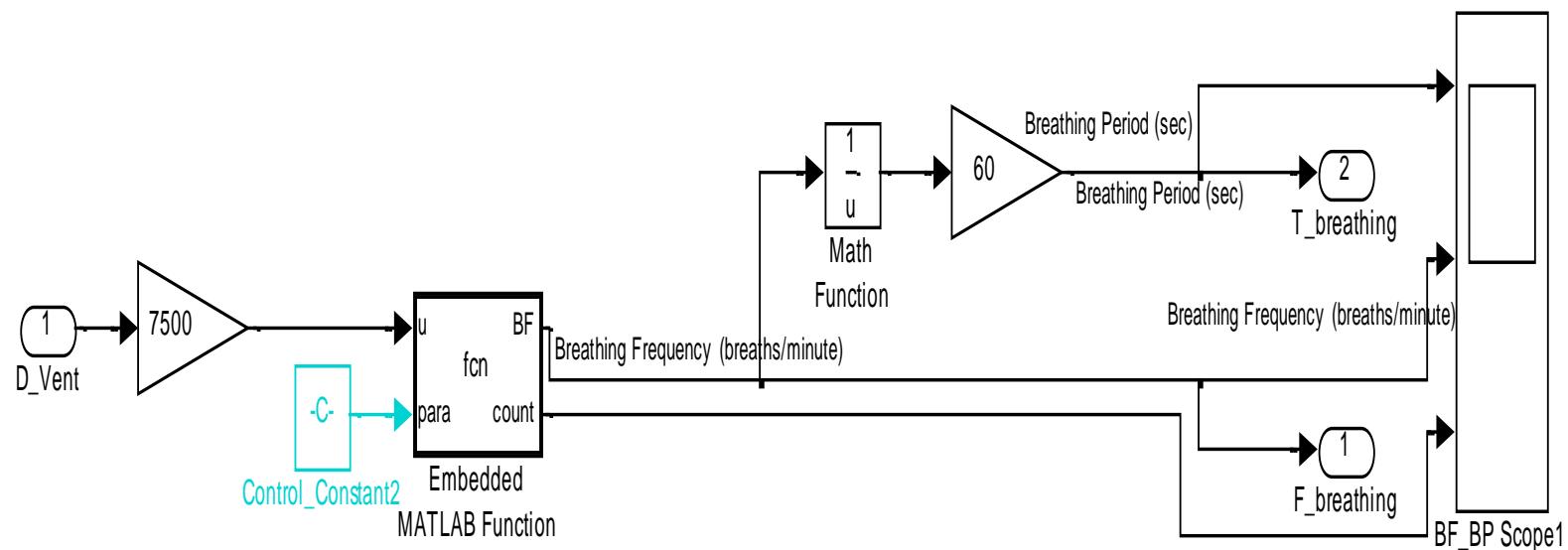
Description

The variable breathing period is controlled from the central neural control system by the total chemoreflex drive [52]. The inspiratory and expiratory periods of a single breath are set to be of equal duration. The ventilatory drive is controlled by central and peripheral chemoreflexes. The combination of ventilatory drive and breathing period determines the neuromuscular drive.

Reference: Duffin J., R.M. Mohan, P. Vasiliou, R. Stephenson, S. Mahamed, "A model of the chemoreflex control of breathing in humans: model parameter measurement," *Respiration Physiology*, vol. 120, pp. 13-26, 2000.

Simulink Model: Variable respiratory rhythm generator



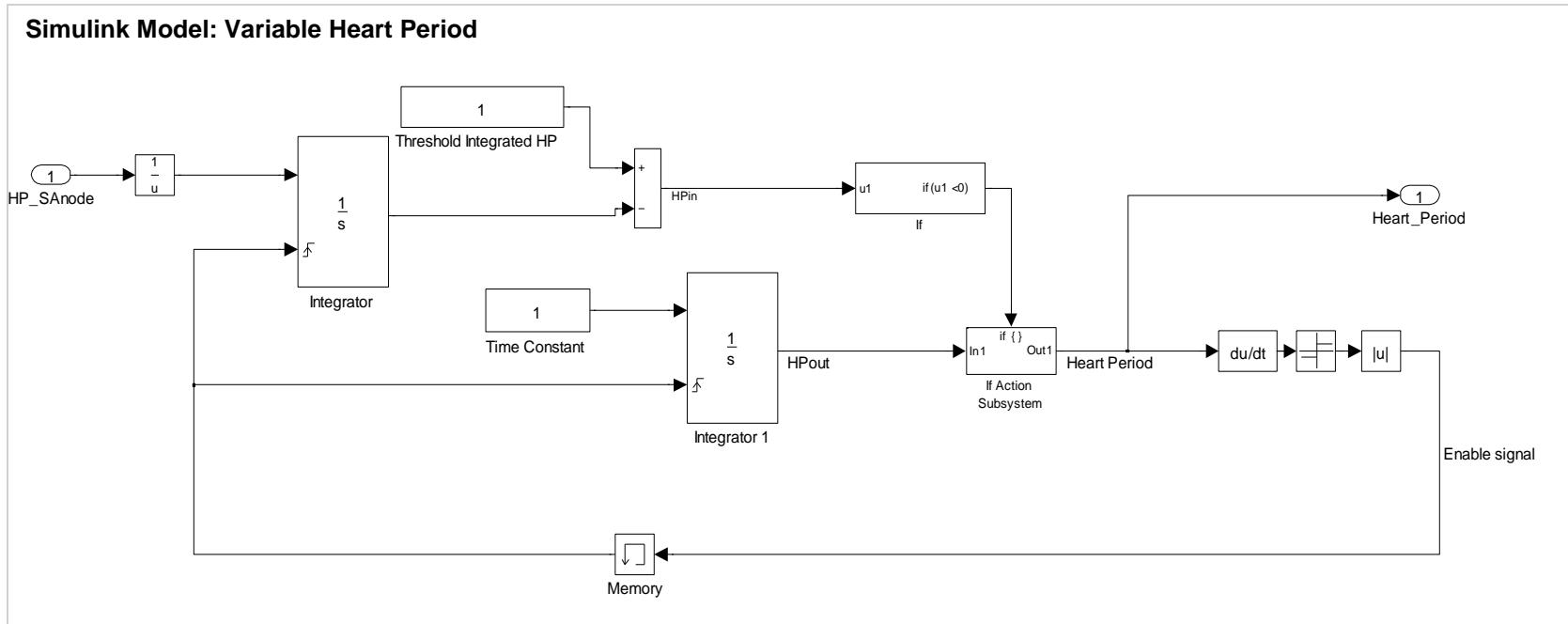
Simulink Model: Ventilatory drive breathing frequency/period

Variable Heart Period (PNEUMA.mdl)

Description

The variable heart period module is modulated by the major reflexes and cardiorespiratory interactions in a closed loop mode. The sinoatrial node is modeled as a simple pacemaker, regulated by the parasympathetic and the beta-sympathetic inputs. The variable heart period is generated from continuous SA output using an integration/saturation mechanism. The beta-sympathetic branch affects the heart rate contractility, thus modulating the systolic period. Greater beta-sympathetic tone increases myocardial elastance and shortens ventricular systole. Each active atria-ventricular compartment is characterized by a time-varying nonlinear elastance function, describing the changes in ventricular elastance due to the beta-sympathetic tone input. The diastolic filling time is the difference between the heart period and systolic period and is thus controlled indirectly. The activation of the right and left hearts is fully synchronized and occurs simultaneously.

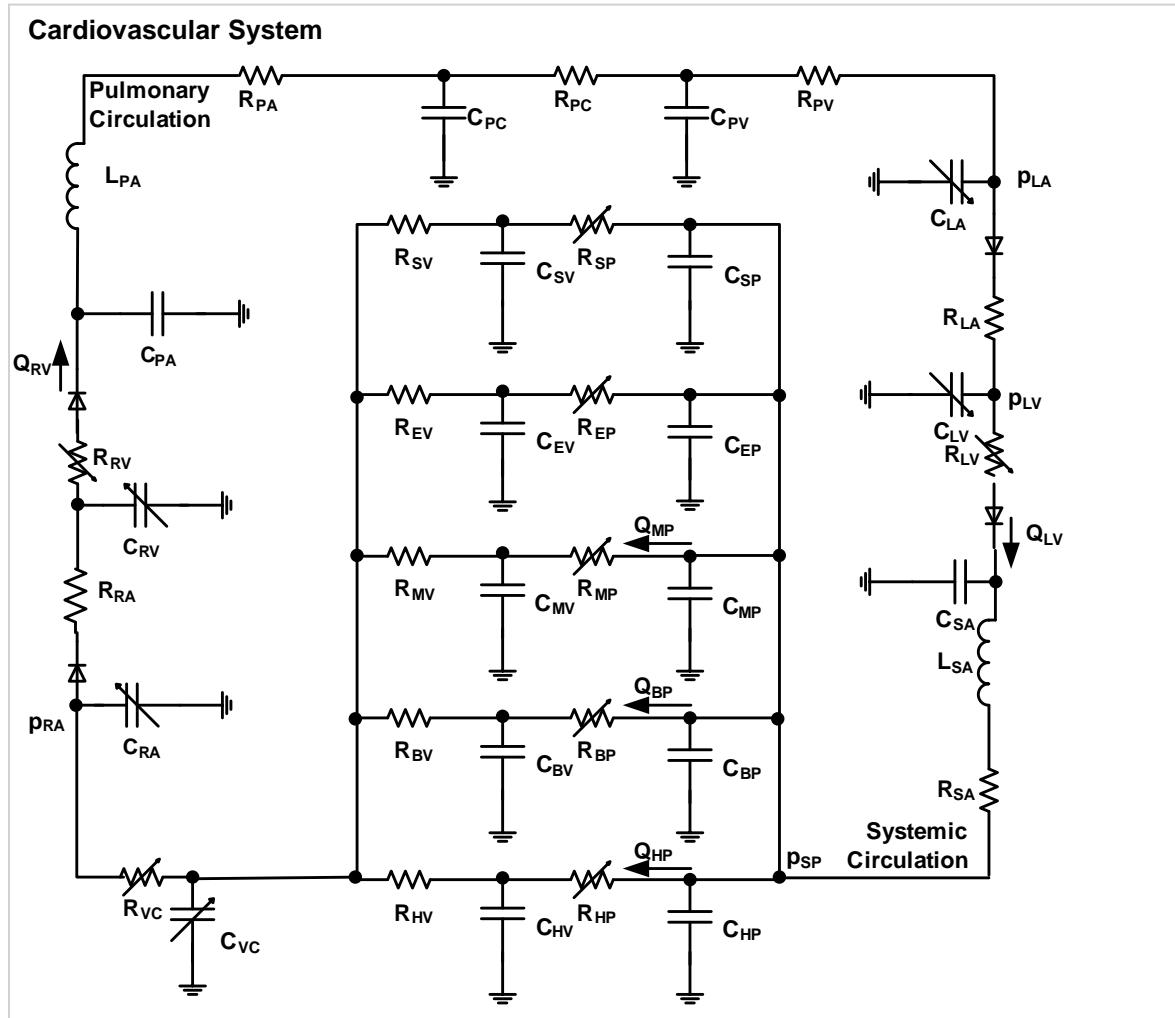
Reference: Dempsey, J.A., Smith, C.A., Eastwood, P.R., Wilson, C.R., Khoo, M.C.K. Sleep induced respiratory instabilities. In: Pack, A.I. (Ed.), *Sleep Apnea Pathogenesis, Diagnosis and Treatment*. Dekker M., New York. 2002.



Cardiovascular System (PNEUMA.mdl)

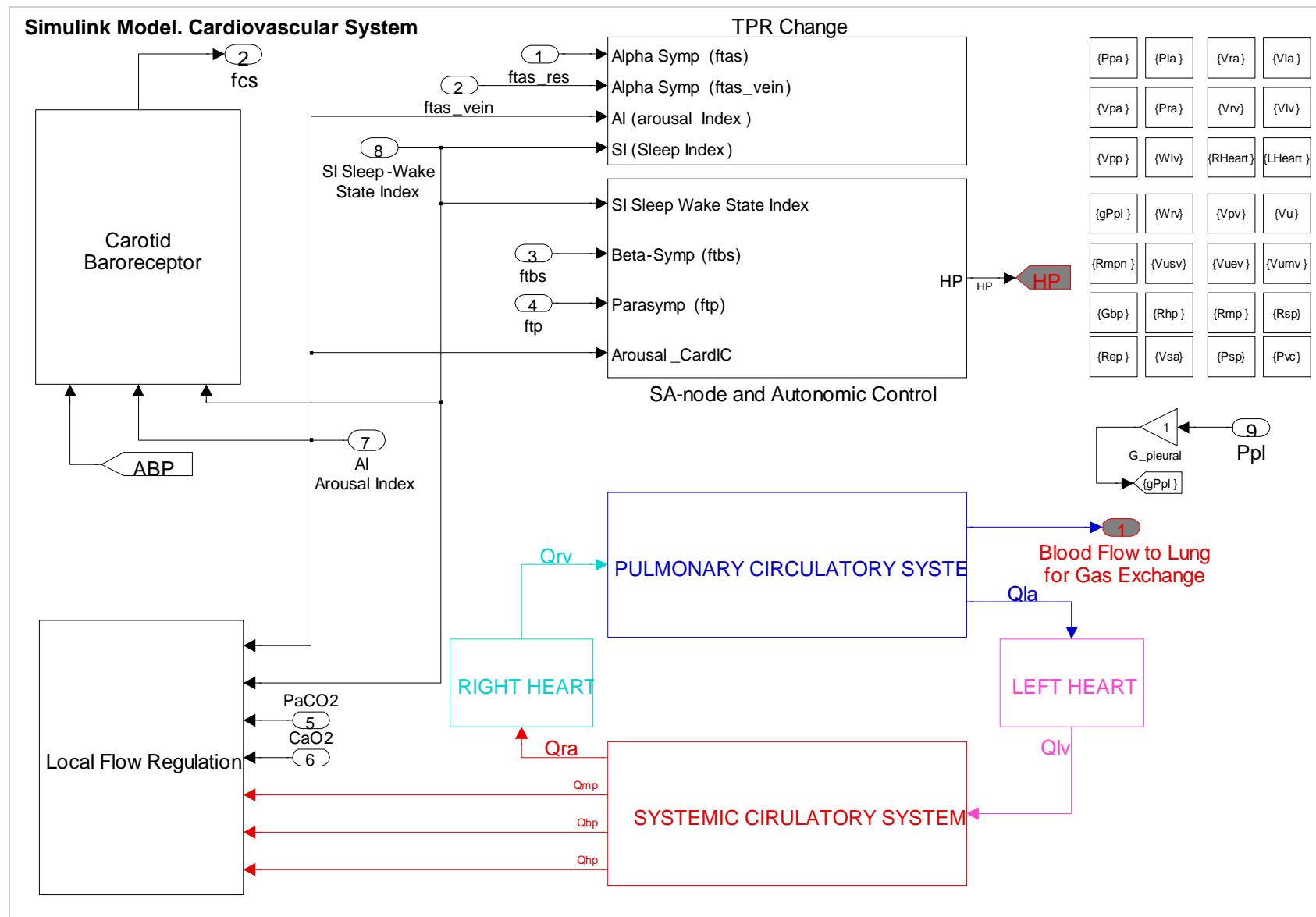
Description

The cardiovascular subsystem is capable of simulating the pulsatile nature of the heart and blood flow through the pulmonary and systemic circulations. Included in the model are descriptions of atria-ventricular mechanics, hemodynamics of the systemic and pulmonary circulations, SA node, change of total peripheral resistance and baroreflex. The inputs for this combined subsystem are the α -sympathetic firing rates, **ftas_res,vein**, β -sympathetic firing rates, **ftbs**, parasympathetic firing rate, **ftp**, arterial **PaCO₂**, **CaO₂**, arousal index, **AI**, sleep-wake state index, **SI**, and the pleural pressure, **Ppl**. To incorporate the effects of pleural pressure changes on the circulatory system we modulate basal blood pressure values for systemic and pulmonary components in thoracic cavity and heart. The output is the arterial blood pressure, **ABP**, heart period, **HP**, cardiac output, **CO**, and blood flow to lung for gas exchange.

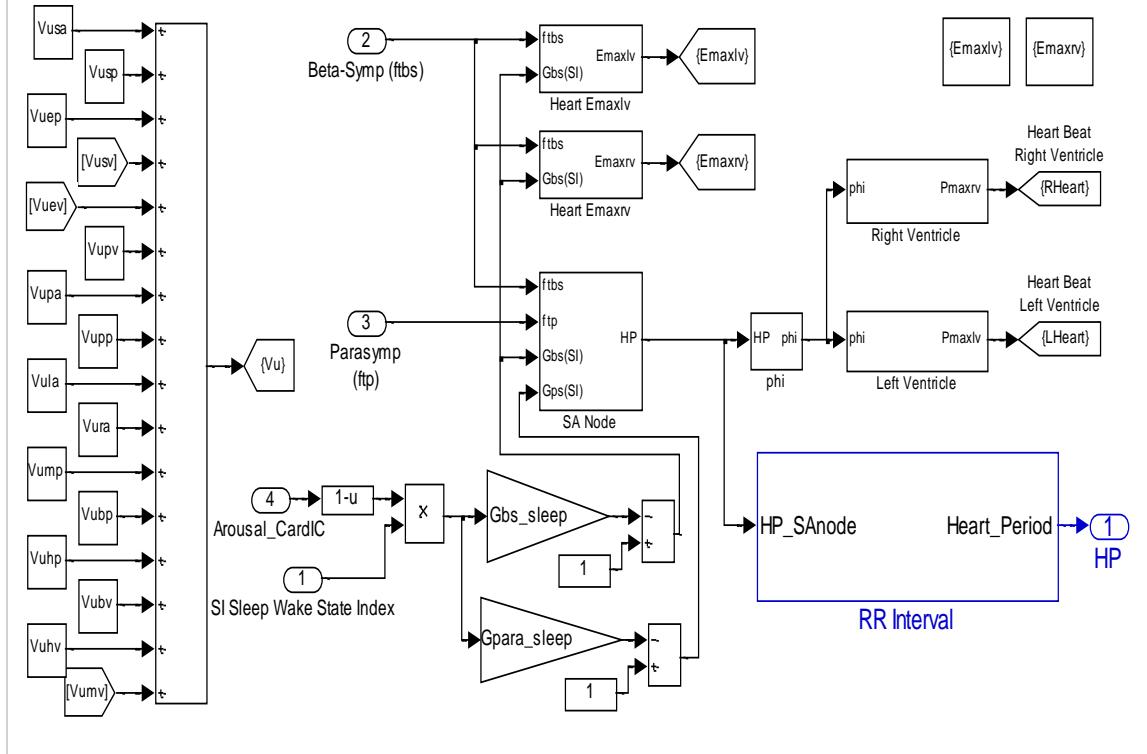


Reference:

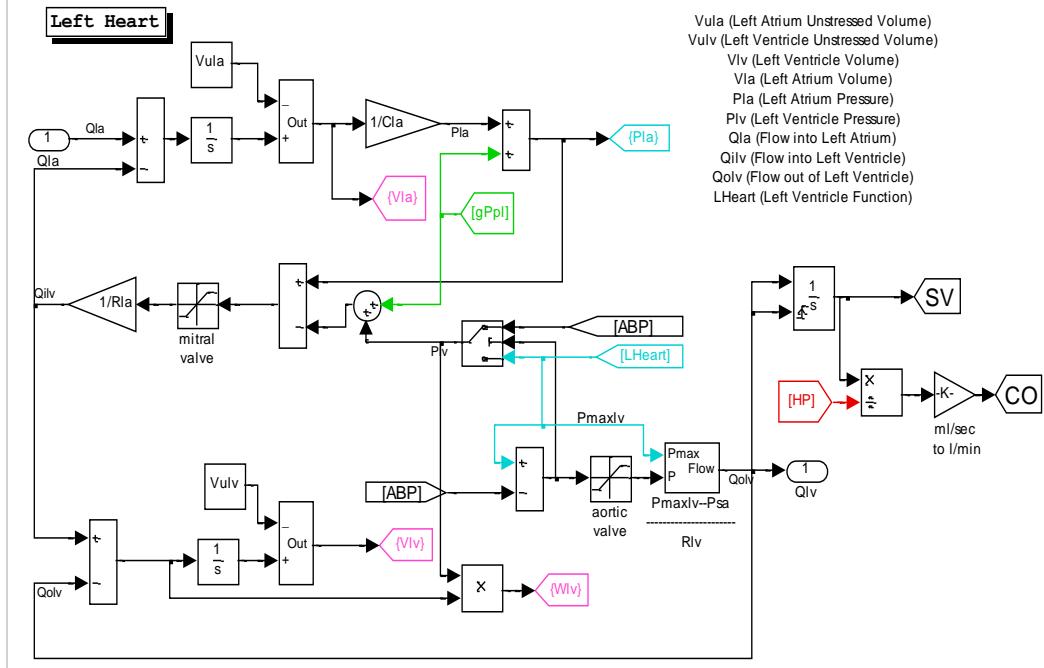
1. Ursino, M. Interaction between carotid baroregulation and the pulsating heart: a mathematical model. *American Journal of Physiology*, 275:H1733-H1747, 1998.
2. Ursino, M., Magosso, E. Acute cardiovascular response to isocapnic hypoxia. I. A mathematical model. *American Journal of Physiology – Heart and Circulatory Physiology*, 279, H149-165, 2000.

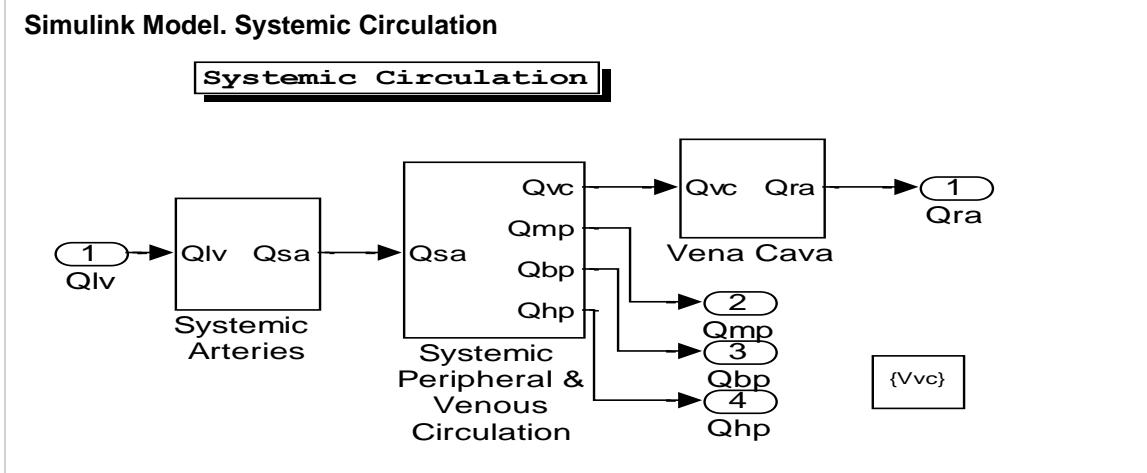
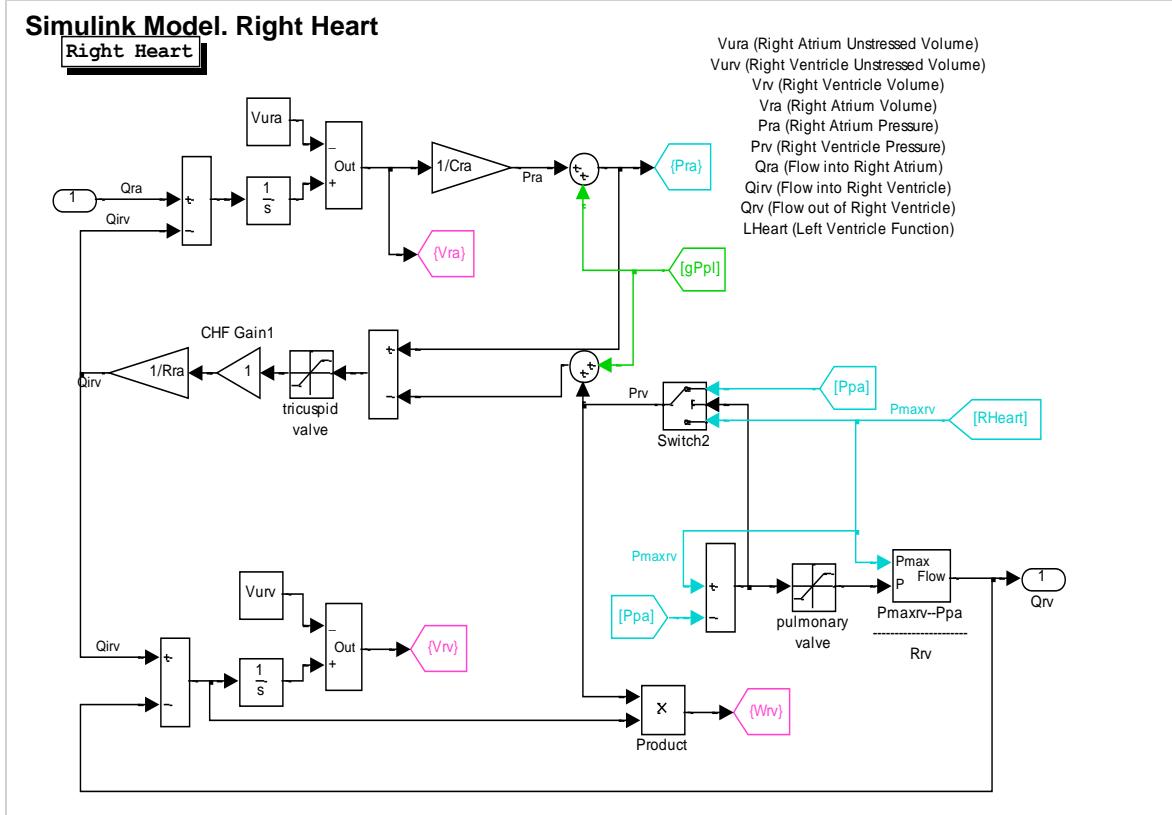


Simulink Model. SA-Node and Autonomic Control

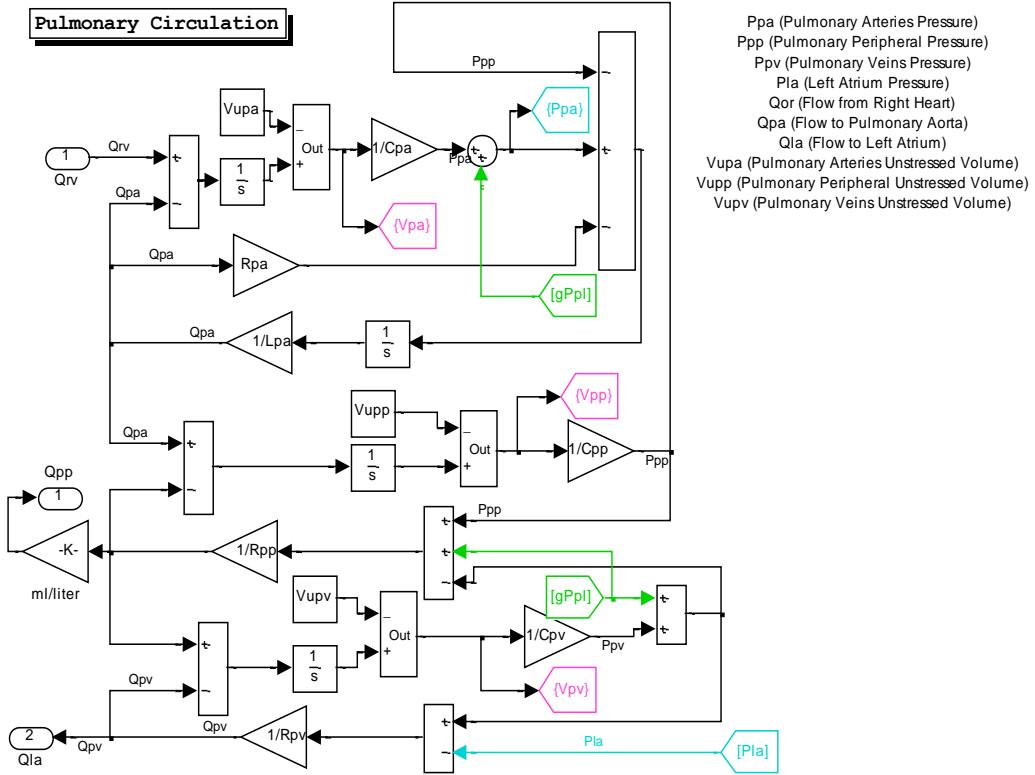


Simulink Model. Left Heart

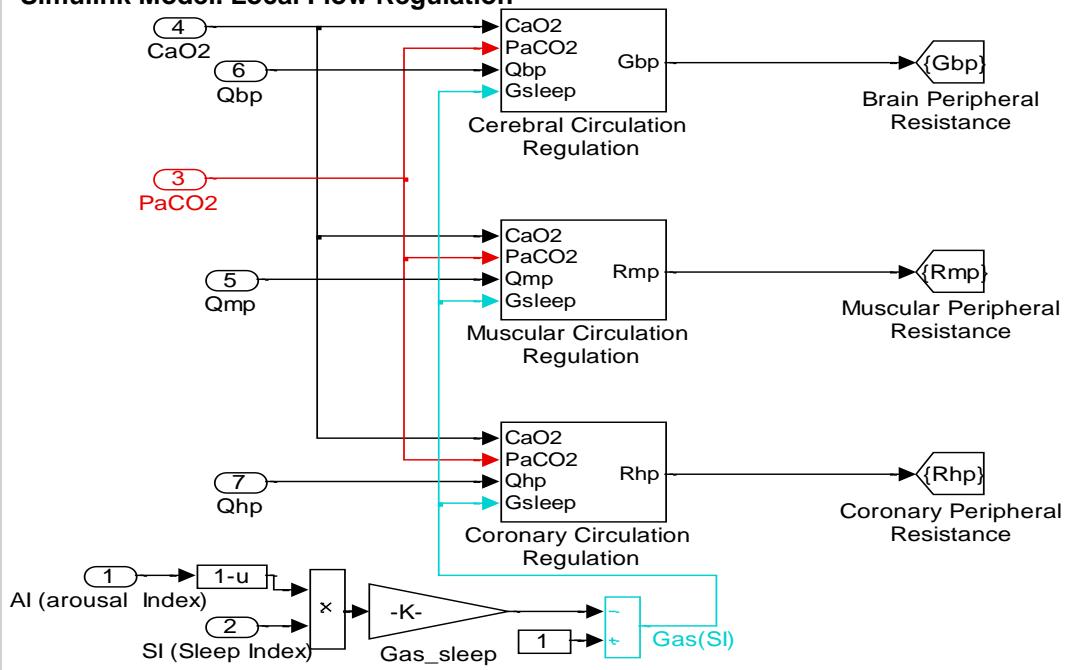




Simulink Model. Pulmonary Circulation



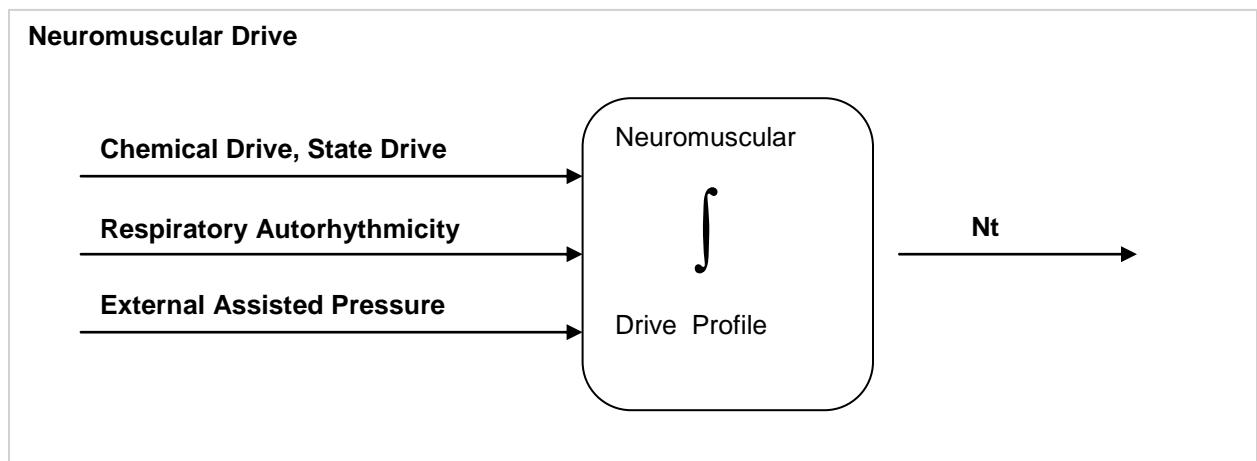
Simulink Model. Local Flow Regulation



Neuromuscular Drive (NeuroMuscular.mdl)

Description

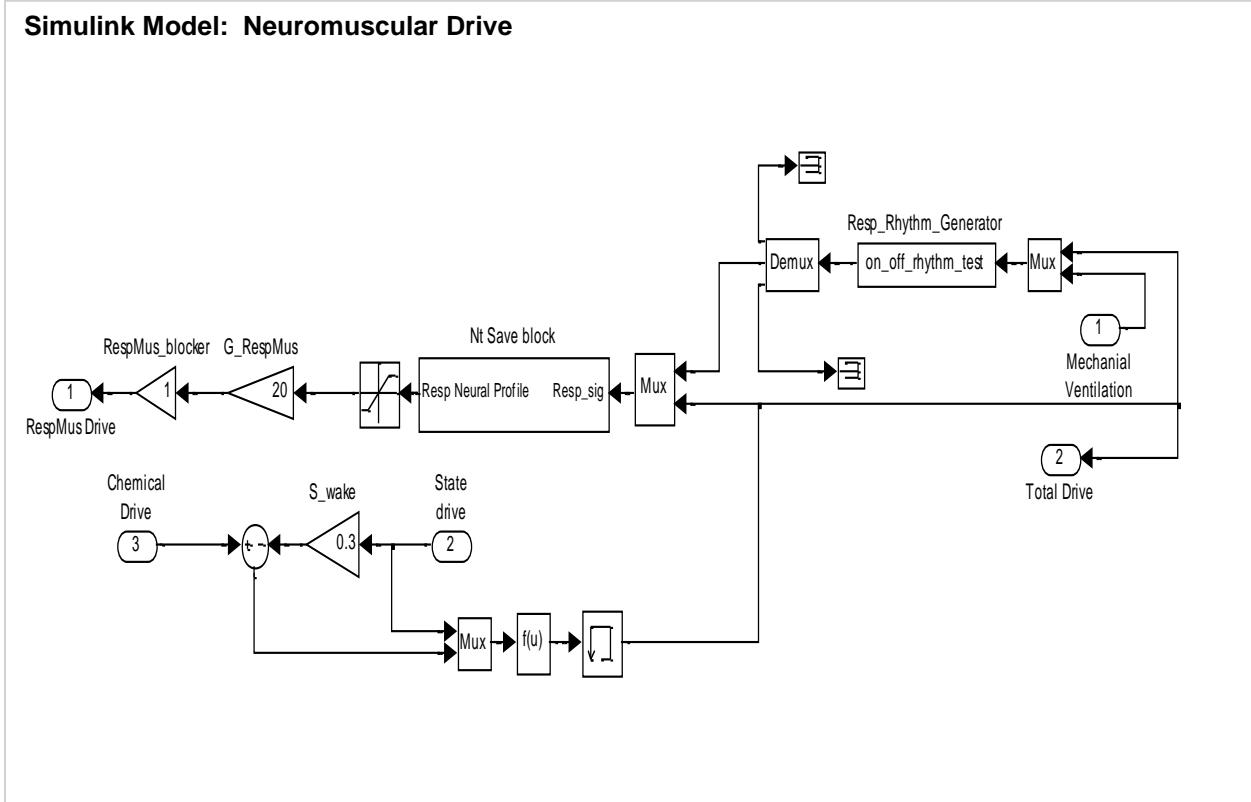
Inspiratory muscular activity is produced by neural drive arising from the respiratory centers. The muscles have to overcome the resistive and elastic forces of the lungs and chestwall to generate the airflow. The muscular drive is modulated by the autorhythmicity, chemical and state drives. In the case of the mechanical assisted ventilation, the internal neural activity will diminish with a period of time. The inputs for this compartment are the chemical drive, Dchemo, external pressure, Dext and the state-related drive, Dstate. The output is the neuromuscular drive, Nt.



Neuromuscular Drive Equations:

$$\text{Respiratory Autorhythmicity} = \text{SquareFund}(TI, TT)$$

$$N(t) = \begin{cases} \int_0^{T_I} D_{total} dt & 0 \leq t \leq T_I \\ 0 & T_I < t \leq T_T \end{cases}$$

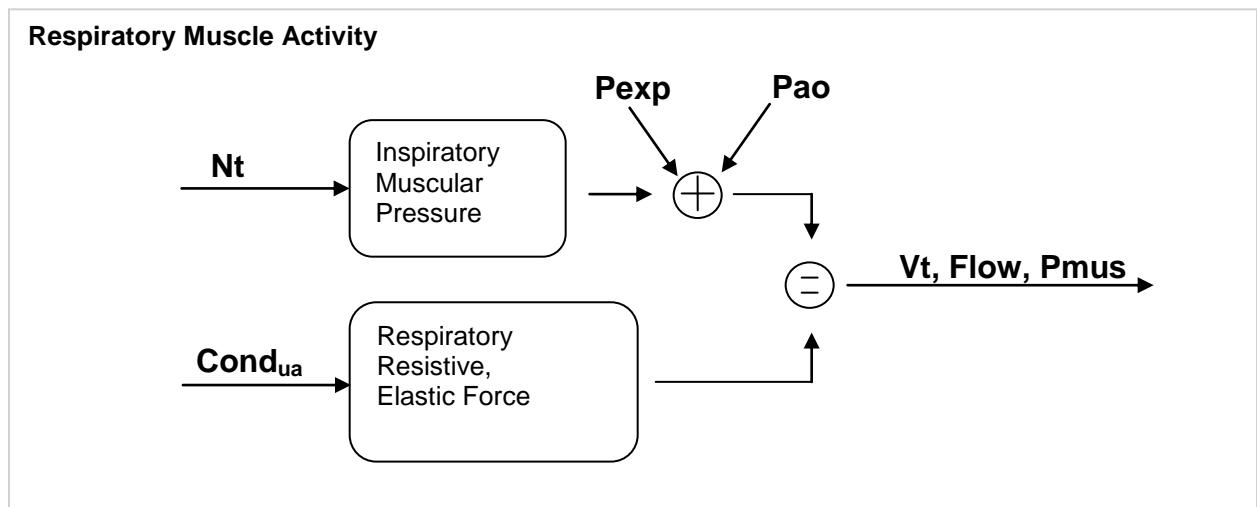


Inputs:	Dchemo	Chemical Drive
	Dext	External drive or pressure
	Dstate	State related Drive
Output:	Nt	Neural-Muscular Drive
Variables:	Gstate	State Drive gain
	TTmean	Breathing Period
	TImean	Inpiration Period
	Inhale	Boolean variable for inhalation

Respiratory Muscle Activity (Pmus_Flow_Younes.mdl)

Description

During the breathing process, the respiratory muscles have to overcome the resistive and the elastic forces of the respiratory system. By equating the force generated from the respiratory muscles with the pressure from the respiratory system, the airflow pattern can be obtained using a simple mechanics model, and tidal volume can be computed from the flow. During normal breathing, expiratory muscular activity is minimum. The inputs are the neural signals, Nt, the upper airway conductance, Cond_{ua}, the expiratory pressure, Pexp and the external pressure, Pao. The outputs are the airflow, Flow, tidal volume, Vt and the muscular pressure, Pmus.



Respiratory Mechanics Equations:

$$P_{isom} = G_{neuromusc} D_{Total}$$

$$Y_{rs} = \frac{Y_{ua}}{1 + (R_{AW} + R_{LT} + R_{CW}) \cdot Y_{ua}}$$

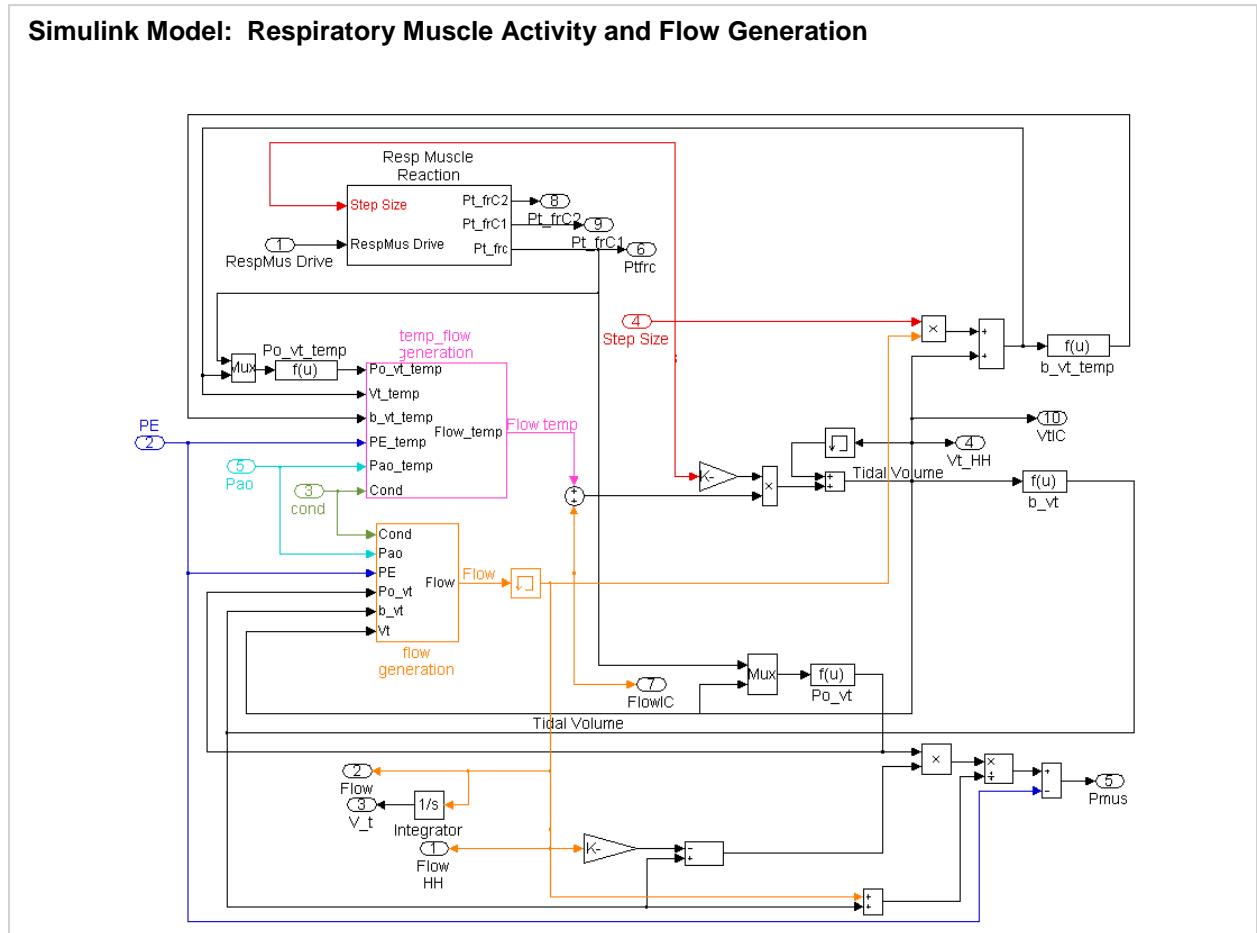
Note: when Yua=0, then Yrs = 0.

$$\dot{V}_t = \frac{\sqrt{(0.25^{P_{isom}(t)e^{-V_t/0.28VC}} \cdot Y_{rs} + b^{V_t} + V_t E_{rs} Y_{rs} - P_{ao} Y_{rs})^2 + 4b^{V_t} (P_{isom} e^{-V_t/0.28VC} Y_{rs} - V_t E_{rs} Y_{rs} + P_{ao} Y_{rs})}}{2}$$

$$- \frac{0.25^{P_{isom}(t)e^{-V_t/0.28VC}} \cdot Y_{rs} + b^{V_t} + V_t E_{rs} Y_{rs} - P_{ao} Y_{rs}}{2}$$

$$\begin{aligned}
 P_{mus} &= \frac{P_{isom} e^{-V_t/0.28VC} (b^V - 0.25V_t)}{(V_t + b^V)} \\
 P_{PL} &= R_{CW} V_t + E_{CW} V_t - P_{mus} \\
 P_{alv} &= R_{LT} V_t + E_{LT} V_t + P_{PL} \\
 V_t &= \frac{\sqrt{(0.25GP(t)e^{-V_t/0.28VC} + b^V + GV_tE + GP_E - GP_{AO})^2 + 4b^V(GP(t)e^{-V_t/0.28VC} - GV_tE - GP_E + GP_{AO})}}{2} \\
 &\quad - \frac{0.25GP(t)e^{-V_t/0.28VC} + b^V + GV_tE + GP_E - GP_{AO}}{2}
 \end{aligned}$$

Reference: Younes, M. and Riddle W. A model for the relation between respiratory neural and mechanical outputs. II. Methods. *Journal of Applied Physiology*, 51(4): 979-989, 1981.

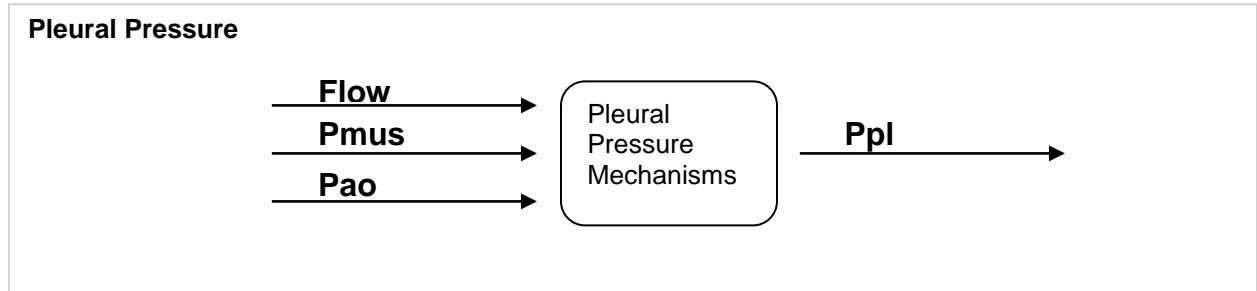


Inputs:	Nt	Neural-Muscular Drive
	Condua	Upper Airway conductance
	Pexp	Expiratory Pressure
	Pao	External Pressure
Outputs:	Vt	Lung Volume
	Flow	Air flow
	Pmus	Muscle Pressure
Variables:	Flowo	Initial air flow
	tau_resp	Inspiratory muscle response time
	delta_t	Integration step time
	VC	Vital Capacity
	Vo	Initial lung volume
	pt_frcIC1	Initial condition for respiratory muscle reaction
	pt_frcIC2	Initial condition for respiratory muscle reaction
	FlowIC	Initial condition for airflow
	VtIC	Initial condition for lung volume

Pleural Pressure(Pleural_Schuessler.mdl)

Description

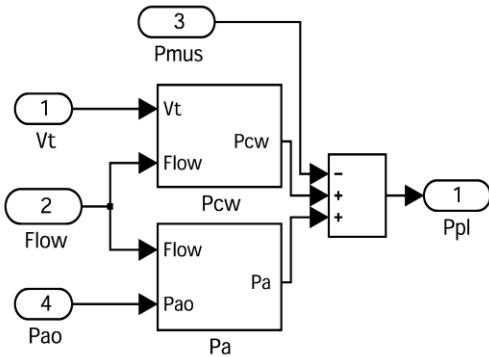
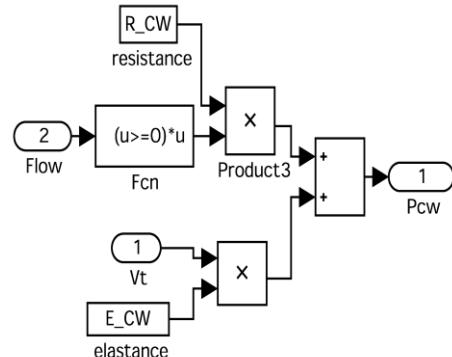
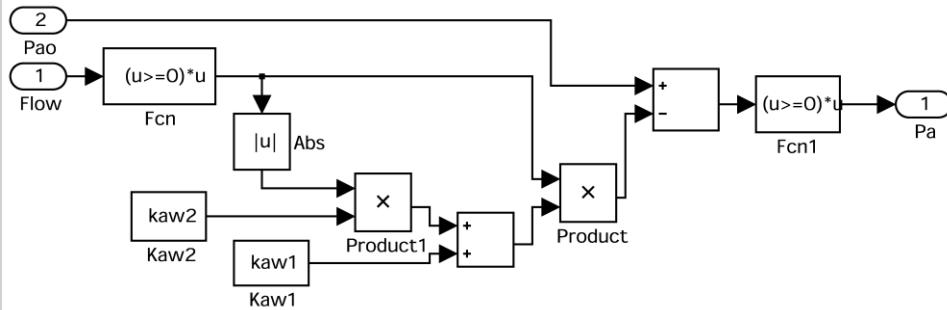
Pleural pressure influences the arterial blood pressure by increasing the venous return and decreasing the cardiac output. The combination of the respiratory muscle force and the static chest wall pressure yields pleural pressure. The inputs are airflow, Flow, muscular pressure, Pmus and external pressure, Pao. The output is the pleural pressure, Ppl.



Pleural Pressure Equation:

$$\begin{aligned}
 P_{PL} = & P_{AO} - \left(K_{1,AW} + K_{2,AW} \left| \dot{V}_t \right| \right) \dot{V}_t - \frac{P_{V_t} (b^{V_t} - 0.25 \dot{V}_t)}{(\dot{V}_t + b^{V_t})} \\
 & - P_E + R_{CW} \dot{V}_t + E_{CW} V_t
 \end{aligned}$$

Reference: Schuessler, T.F., Gottfried, S.B. and Bates, J.H.T. A model of the spontaneously breathing patient: applications to intrinsic PEEP and work of breathing. *Journal of Applied Physiology*, 82(5): 1694-1703, 1997.

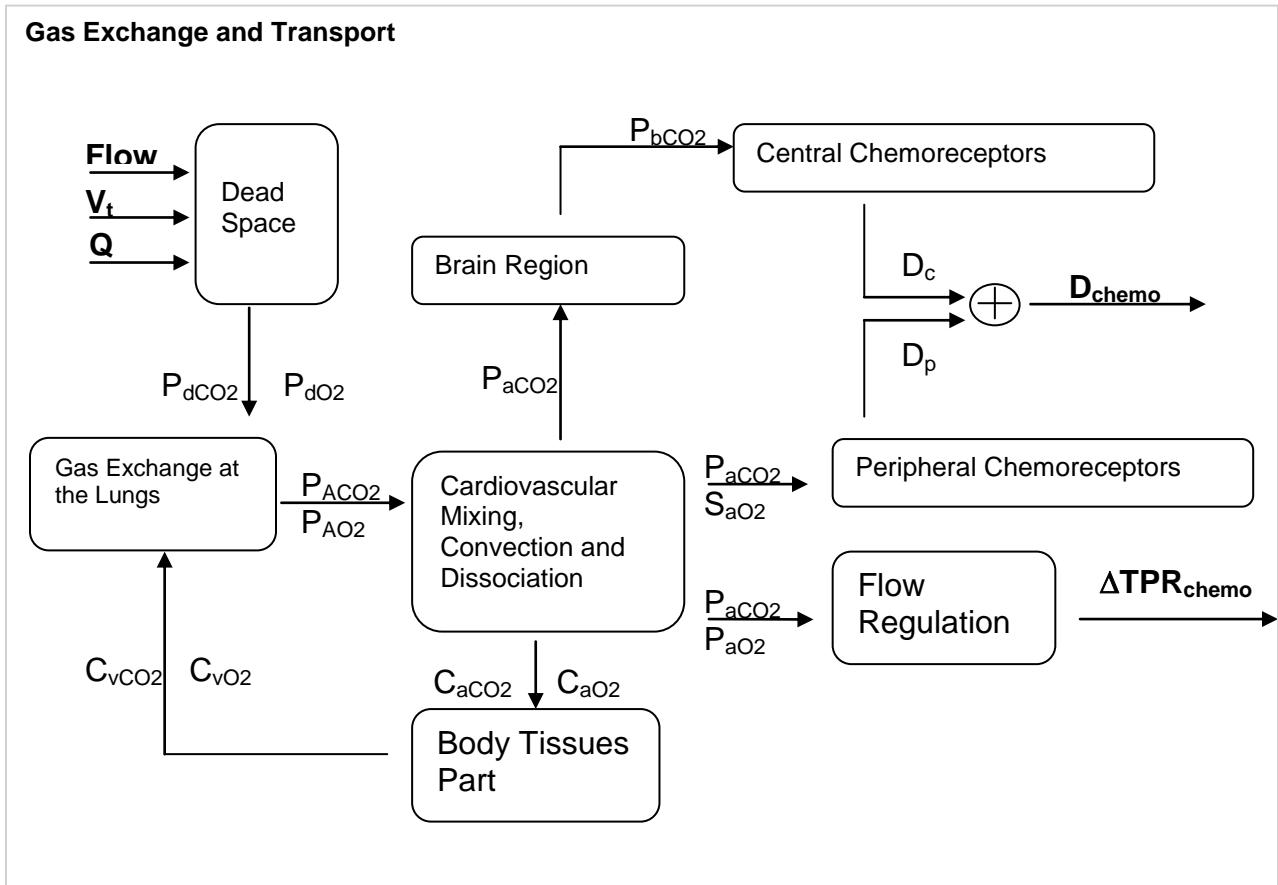
Simulink Model: Pleural Pressure**Simulink Model: Chest Wall Mechanics****Simulink Model: Airway Pressure**

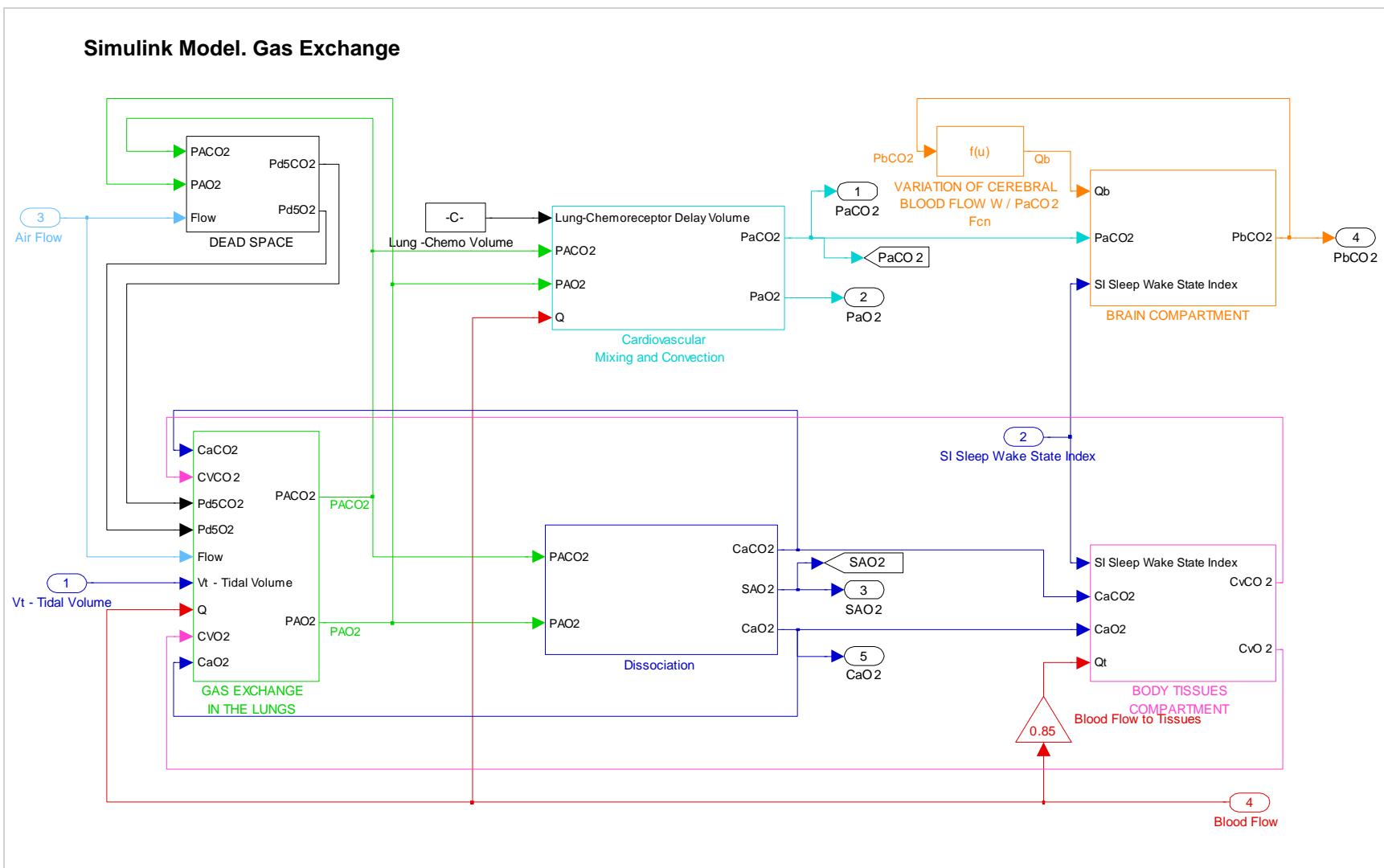
Inputs:	Flow	Air flow
	Pmus	Inspiratory muscle pressure
	Pao	External Pressure
Output:	Ppl	Pleural Pressure
Variables:	Rcw	Chest Wall resistance
	Ecw	Chest Wall elastance
	k1,aw	Constant for upper airway pressure
	k2,aw	Constant for lower airway pressure

Gas Exchange and Transport (Gas_Exchange.mdl)

Description

This subsystem models gas transport through the dead space, CO₂ and O₂ exchange in the alveoli, the CO₂ and O₂ dissociation curves, and the transport of CO₂ and O₂ in the blood to the chemoreceptors along with vascular mixing. Also included in this module are CO₂ exchange in the brain compartment, gas exchange in the body tissues, conversion of blood gases into respiratory drive by the chemoreflexes, and chemoreflex effects on peripheral vascular resistance. The inputs are airflow, **Flow**, tidal volume, **V_t** and cardiac output, **CO** (in this case, it is synonymous with blood flow, **Q**). The output is the chemoreflex-related ventilatory drive, **D_{chemo}** and chemoreflex modulation of total peripheral resistance, **ΔTPR_{chemo}**.

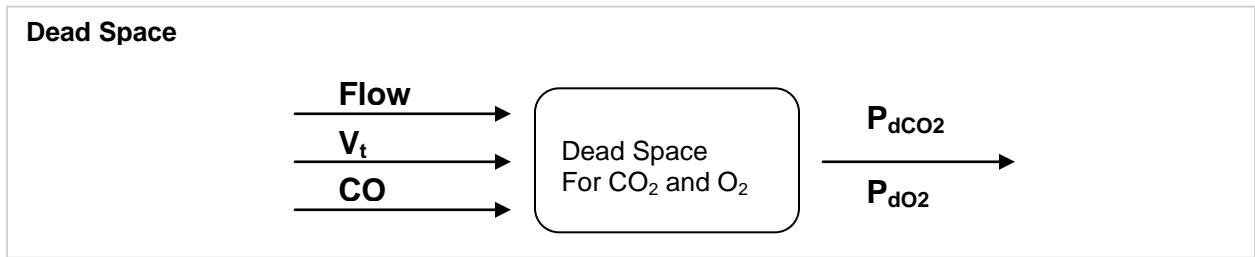




Dead Space (Dead_Space_Khoo.mdl)

Description

We assume that no gas exchange with blood occurs in the dead space. The inputs are airflow, **Flow**, tidal volume, **V_t** and blood flow, **Q**. The outputs are the CO₂, **P_{dCO2}** and the O₂, **P_{dO2}** partial pressure for the dead space.



Dead Space Equations:

CO₂

Inspiration

$$\dot{V}_{d(1)} \dot{P}_{d(1)CO_2} = \dot{V}[P_{I_{CO_2}} - P_{d(1)CO_2}]$$

$$\dot{V}_{d(i)} \dot{P}_{d(i)CO_2} = \dot{V}[P_{d(i-1)CO_2} - P_{d(i)CO_2}] \quad 2 \leq i \leq 5$$

Expiration

$$\dot{V}_{d(i)} \dot{P}_{d(i)CO_2} = \dot{V}[P_{d(i+1)CO_2} - P_{d(i)CO_2}] \quad 1 \leq i \leq 4$$

$$\dot{V}_{d(5)} \dot{P}_{d(5)CO_2} = \dot{V}[P_{A_{CO_2}} - P_{d(5)CO_2}]$$

O₂

Inspiration

$$\dot{V}_{d(1)} \dot{P}_{d(1)O_2} = \dot{V}[P_{I_{O_2}} - P_{d(1)O_2}]$$

$$\dot{V}_{d(i)} \dot{P}_{d(i)O_2} = \dot{V}[P_{d(i-1)O_2} - P_{d(i)O_2}] \quad 2 \leq i \leq 5$$

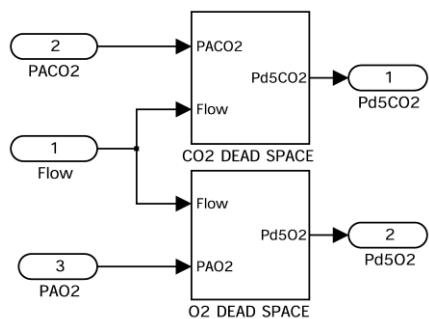
Expiration

$$\dot{V}_{d(i)} \dot{P}_{d(i)O_2} = \dot{V}[P_{d(i+1)O_2} - P_{d(i)O_2}] \quad 1 \leq i \leq 4$$

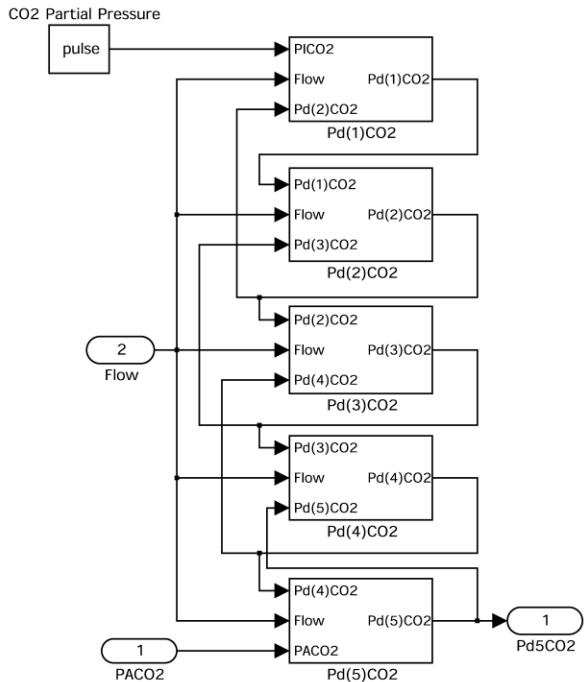
$$\dot{V}_{d(5)} \dot{P}_{d(5)O_2} = \dot{V}[P_{A_{O_2}} - P_{d(5)O_2}]$$

Reference: Khoo, M.C.K., A model-based evaluation of the single-breath CO₂ ventilatory response test. *Journal of Applied Physiology*, 68(1):393-399, 1990.

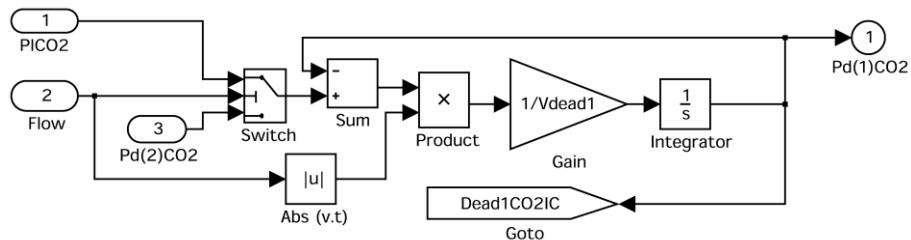
Simulink Model: Entire Dead Space subsystem



Dead Space Compartments for CO₂



Individual Dead Space Compartment for CO₂

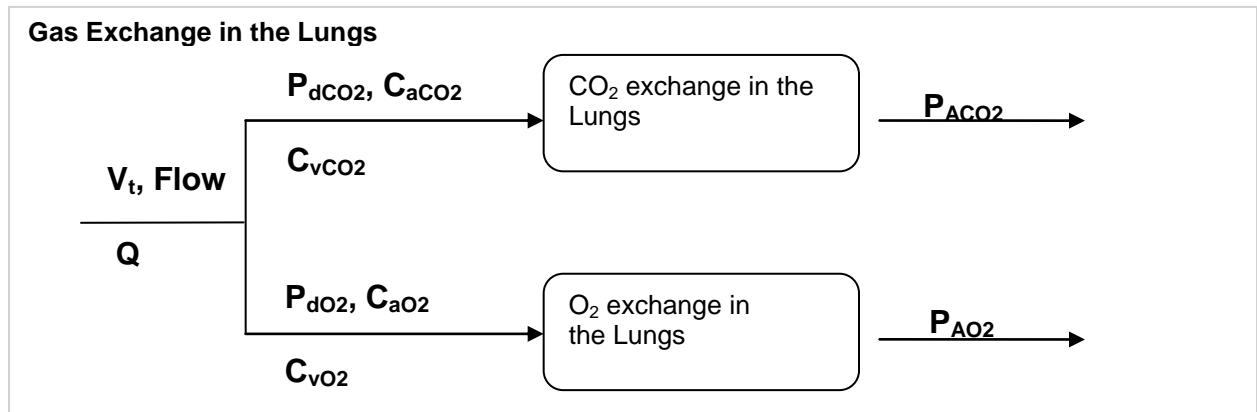


Note: Dead Space Compartments for CO₂ and O₂ designs are the same. Only Part of CO₂ implementations are shown as examples.

Inputs:	Flow	Air flow
	V_t	Lung Volume
	CO	Cardiac Output
Outputs:	P_{aco2}	Dead Space CO ₂ partial pressure
	P_{ao2}	Dead Space O ₂ partial pressure
Variables:	Dead_{(i),co2I}	Initial condition for i th CO ₂ dead space
	C	
	Dead_{(i),o2I}	Initial condition for i th O ₂ dead space
	C	
	V_{d(i)}	i th dead space volume
	P_{I,CO2}	Inspiratory CO ₂ partial pressure
	P_{I,O2}	Inspiratory O ₂ partial pressure

Alveolar Gas Exchange (Lungs_Khoo.mdl)

CO_2 and the O_2 exchange in the lungs are both modeled assuming first-order dynamics. The rate of exchange is affected by the gas concentration in the blood, the gas partial pressure and the blood flow rate. The CO_2 storage space is larger than that for O_2 to account for the larger capacity of lung tissue and lung water for CO_2 . The inputs are the CO_2 , P_{dCO_2} and O_2 , P_{dO_2} partial pressure for dead space, arterial CO_2 , C_{aCO_2} and O_2 , C_{aO_2} concentration, venous CO_2 , C_{vCO_2} and O_2 , C_{vO_2} concentration, tidal volume, V_t , airflow, **Flow** and blood flow, Q . The outputs are alveolar CO_2 , P_{ACO_2} and O_2 , P_{AO_2} partial pressure.



Gas Exchange in the Lungs Equations:

Inspiration

$$\dot{V}_{\text{co}_2} \dot{P}_{\text{Aco}_2} = [863 \dot{Q}(C_{\text{vco}_2} - C_{\text{aco}_2}) + \dot{V}_A(P_{\text{d(5)co}_2} - P_{\text{Aco}_2})]$$

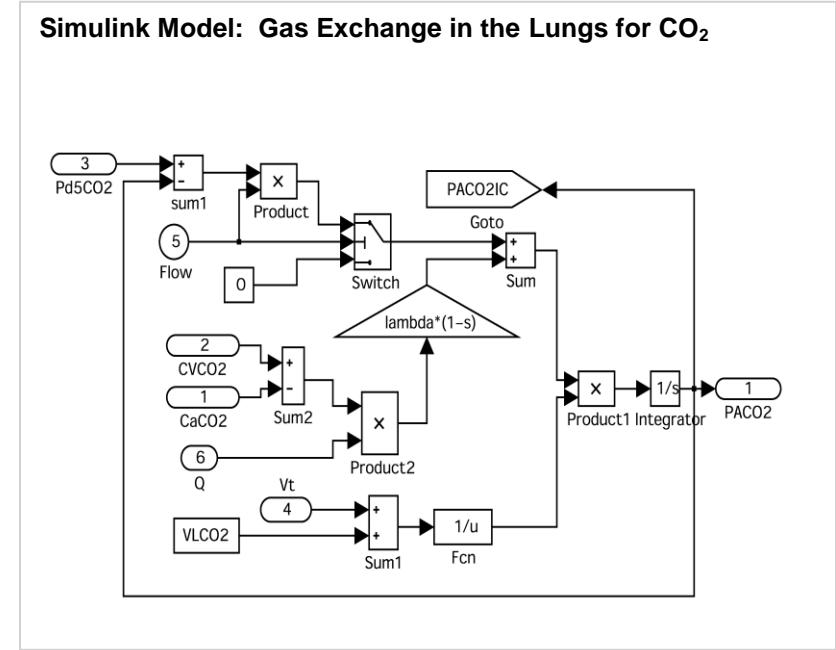
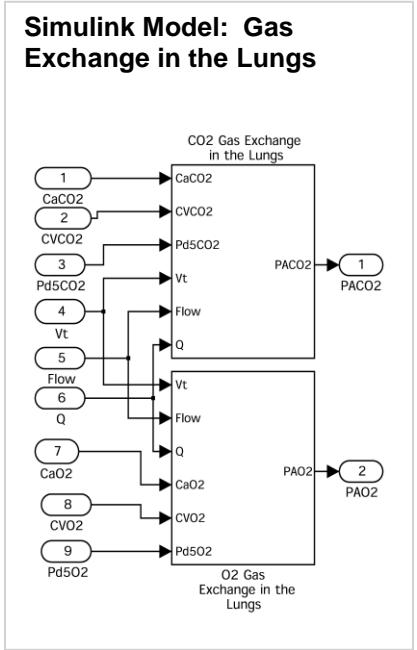
$$\dot{V}_{\text{o}_2} \dot{P}_{\text{Ao}_2} = [863 \dot{Q}(C_{\text{vo}_2} - C_{\text{ao}_2}) + \dot{V}_A(P_{\text{d(5)o}_2} - P_{\text{Ao}_2})]$$

Expiration

$$\dot{V}_{\text{co}_2} \dot{P}_{\text{Aco}_2} = [863 \dot{Q}(C_{\text{vco}_2} - C_{\text{aco}_2})]$$

$$\dot{V}_{\text{o}_2} \dot{P}_{\text{Ao}_2} = [863 \dot{Q}(C_{\text{vo}_2} - C_{\text{ao}_2})]$$

Reference: Khoo, M.C.K., A model-based evaluation of the single-breath CO_2 ventilatory response test. *Journal of Applied Physiology*, 68(1):393-399, 1990.



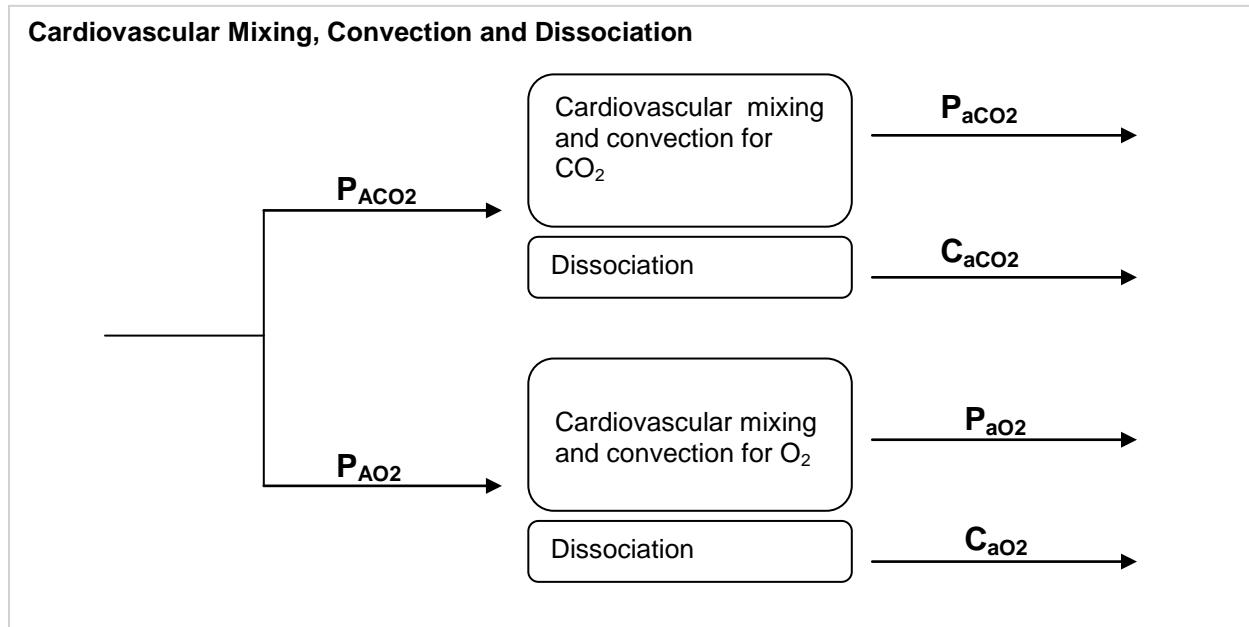
Note: O₂ compartment is the same implementation as CO₂ and it is not shown here.

Inputs:	$P_{d\text{CO}_2}$	Dead Space CO ₂ partial pressure
	$P_{d\text{O}_2}$	Dead Space O ₂ partial pressure
	$C_{a\text{CO}_2}$	Arterial CO ₂ concentration
	$C_{a\text{O}_2}$	Arterial O ₂ concentration
	$C_{v\text{CO}_2}$	Venous CO ₂ concentration
	$C_{v\text{O}_2}$	Venous O ₂ concentration
	V_t	Tidal volume
	Flow	Airflow
	CO	Cardiac output
Outputs:	P_{ACO_2}	Alveolar CO ₂ partial pressure
	P_{AO_2}	Alveolar O ₂ partial pressure
Variables:	V_{co_2}	Lungs storage volume for CO ₂
	V_{o_2}	Lungs storage volume for O ₂
	P_{Aco2IC}	Initial condition for Partial CO ₂ pressure
	P_{Ao2IC}	Initial condition for Partial O ₂ pressure
	s	Pulmonary shunt
	λ	Concentration / Pressure conversion

Cardiovascular Mixing, Convection and Dissociation (Cardio_Mix_Lange.mdl, Dissociation_Spencer.mdl)

Description

This module includes effects for pulmonary shunt, convection and mixing in the heart and vasculature, as well as the delay taken for arterial blood to travel from the gas exchange site to the chemoreceptors. The mixing and convection processes are affected by the blood flow rate and are modeled assuming a second order dynamic system. Partial pressures are converted to gas concentration in the blood, using the blood-gas dissociation equations. The inputs for this compartment are the alveolar CO₂, P_{ACO₂} and O₂, P_{Ao₂} partial pressure. The outputs are the arterial CO₂, P_{aCO₂} and O₂, P_{aO₂} partial pressure.



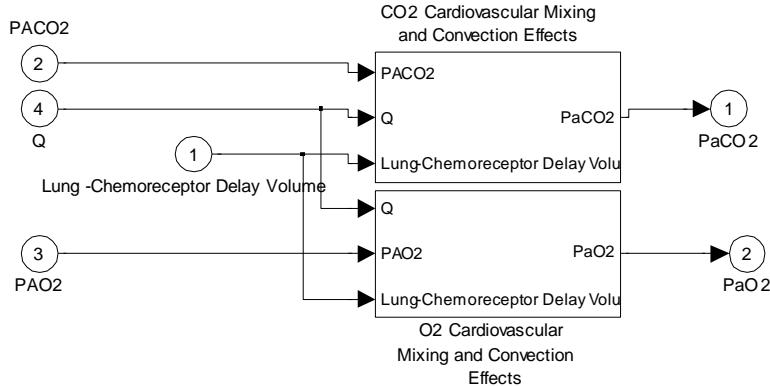
Cardiovascular Mixing Equations:

$$\ddot{P}_{aCO_2} = \frac{1}{(T1*T2)} [P_{ACO_2}(t - T_a) - (T1+T2) \dot{P}_{aCO_2} - P_{aCO_2}]$$

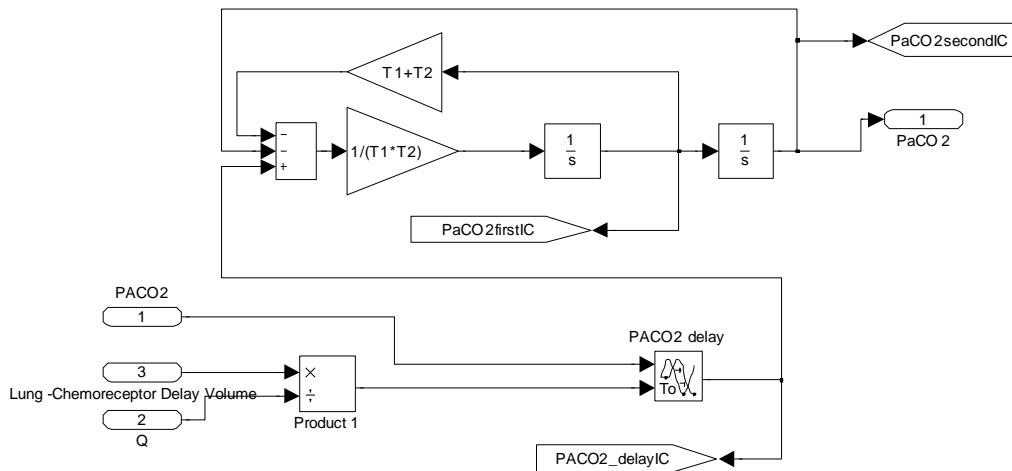
$$\ddot{P}_{ao_2} = \frac{1}{(T1*T2)} [P_{Ao_2}(t - T_a) - (T1+T2) \dot{P}_{ao_2} - P_{ao_2}]$$

Reference: Lange, R.L., Horgan, J.D., Botticelli, J.T., Tsagaris, T, Carlisle, R.P., and Kuida.H., Pulmonary to arterial circulatory transfer function: importance in respiratory control. *Journal of Applied Physiology*, 21(4):1281-1291, 1966.

Simulink Model: Cardiovascular Mixing



Simulink Model: Cardiovascular Mixing for CO₂



Note: O₂ implementation is the same as CO₂.

Cardiovascular Convection Equation:

$$T_a = \frac{K_{dp}}{Q}$$

Inputs:	P _A CO ₂	Alveolar CO ₂ partial pressure
	P _A O ₂	Alveolar O ₂ partial pressure
Outputs:	P _a CO ₂	Arterial CO ₂ partial pressure
	P _a O ₂	Arterial O ₂ partial pressure
Variables:	K _{dp}	Peripheral Chemoreceptors delay time constant
	T ₁	Time constant for cardiovascular mixing
	T ₂	Time constant for cardiovascular mixing
	P _a O ₂ firstIC	Initial condition for first order P _a O ₂ system
	P _a O ₂ secondIC	Initial condition for second order P _a O ₂ system

P_{aCO2firstIC}	Initial condition for first order P _{aco2} system
P_{aCO2secondIC}	Initial condition for second order P _{aco2} system
P_{aO2_delayIC}	Initial condition for O ₂ convection
P_{aco2_delayIC}	Initial condition for CO ₂ convection

Dissociation Equations:

$$C_{O_2} = \bar{C}_{O_2} \frac{F_{O_2}^{1/a_1}}{1 + F_{O_2}^{1/a_1}}$$

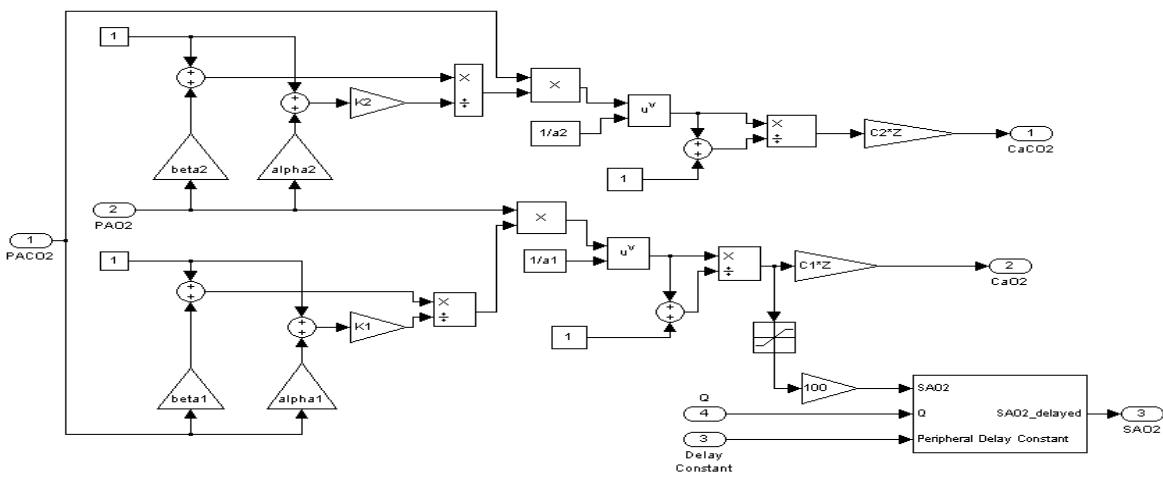
$$C_{CO_2} = \bar{C}_{CO_2} \frac{F_{CO_2}^{1/a_2}}{1 + F_{CO_2}^{1/a_2}}$$

$$F_{O_2} = \frac{P_{AO_2} (1 + \beta_1 P_{ACO_2})}{K_1 (1 + \alpha_1 P_{ACO_2})}$$

$$F_{CO_2} = \frac{P_{ACO_2} (1 + \beta_2 P_{AO_2})}{K_2 (1 + \alpha_2 P_{AO_2})}$$

Reference: Spencer, J.L., Firouztale, E., and Mellins, R.B. "Computational Expressions For Blood Oxygen and Carbon Dioxide Concentrations", *Annals of Biomedical Engineering*, Vol 7, pp. 59-66, 1979.

Simulink Model: Dissociation

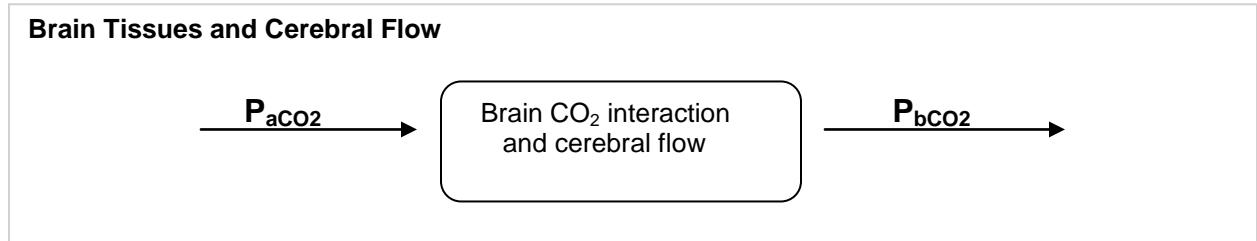


Inputs:	P_{ACO₂}	Alveolar CO ₂ partial pressure
	P_{AO₂}	Alveolar O ₂ partial pressure
Outputs:	P_{aCO₂}	Arterial CO ₂ partial pressure
	P_{aO₂}	Arterial O ₂ partial pressure
	Z	Molar conversion factor
	C₁	Maximum concentration of hemoglobin-bound oxygen
	C₂	Maximum carbon dioxide concentration
	a₁	Parameter in O ₂ dissociation equation
	a₂	Parameter in CO ₂ dissociation equation
	alpha₁	Parameter in O ₂ dissociation equation
	alpha₂	Parameter in CO ₂ dissociation equation
	K₁	Parameter in O ₂ dissociation equation
	K₂	Parameter in CO ₂ dissociation equation
	beta₁	Parameter in O ₂ dissociation equation
	beta₂	Parameter in CO ₂ dissociation equation
	S_{aCO₂_delayI}	Initial Condition for Oxygen Saturation Delay
	C	

Brain Compartment (Brain_Khoo.mdl)

Description

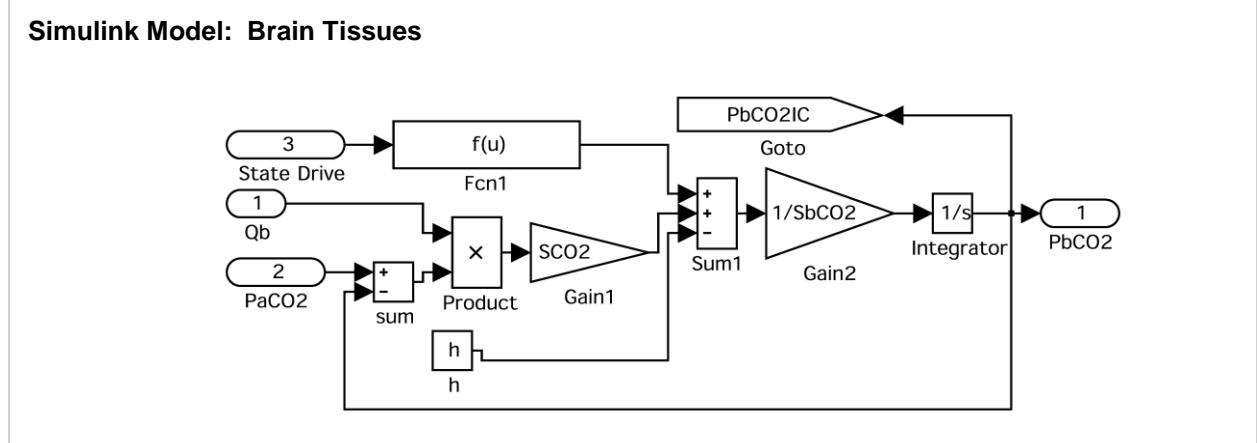
Cerebral flow is highly sensitive to changes of the CO₂ tension in the brain. The brain CO₂ tension is controlled by the metabolic rate and the blood flow rate. The inputs for this compartment are the arterial CO₂ partial pressure, P_{aCO₂} and blood flow in the brain region, Q_b. The output is the brain arterial CO₂ partial pressure, P_{bCO₂}.



Cerebral Flow Equation:

$$\dot{S}_{bCO_2} \dot{P}_{bCO_2} = [MR_{bCO_2} + \dot{Q}_b \dot{S}_{CO_2} (P_{aCO_2} - P_{bCO_2}) - h]$$

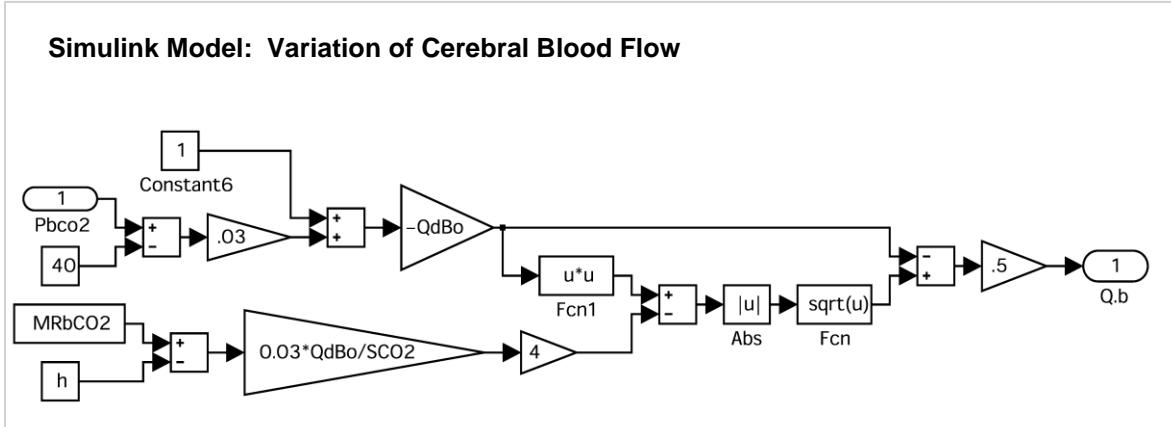
Reference: Read, D.J.C. and Leigh, J. Blood-brain tissue Pco₂ relationships and ventilation during rebreathing. *Journal of Applied Physiology*, 23(1):53-70, 1967.



Brain Tissues Equation:

$$\dot{Q}_b^2 - [1 + 0.03(P_{bCO_2} - 40)] \dot{Q}_b + 0.03(MR_{bCO_2} - h) \dot{Q}_b / \dot{S}_{CO_2} = 0$$

Reference: Khoo, M.C.K., A model-based evaluation of the single-breath CO₂ ventilatory response test. *Journal of Applied Physiology*, 68(1):393-399, 1990.

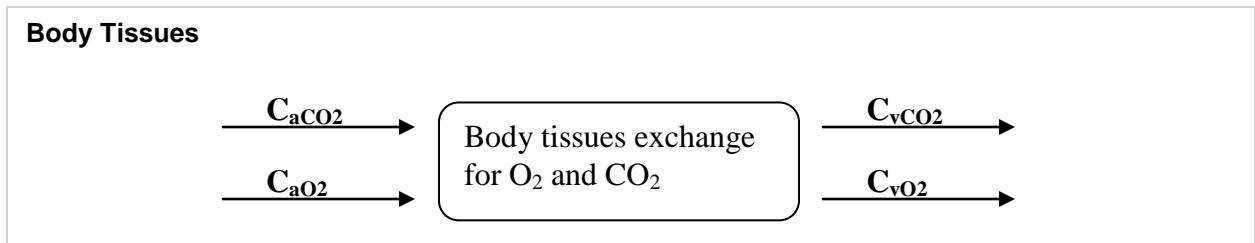


Input:	$P_{a\text{CO}_2}$	arterial CO ₂ partial pressure
Output:	$P_{b\text{CO}_2}$	brain arterial CO ₂ partial pressure
Variables:	$\text{MR}_{\text{bco}2}$	Metabolic production rate for CO ₂ in the brain tissue
	$S_{\text{co}2}$	Dissociation slope for CO ₂ in the blood
	$S_{\text{bco}2}$	Dissociation slope for CO ₂ in the brain tissue
	$P_{\text{bco}2\text{IC}}$	Initial condition for partial CO ₂ pressure from the brain

Body Tissues Compartment (Body_Khoo.mdl)

Description

Gas exchange that occurs outside of the lungs and the brain is modeled as taking place in a single compartment. The rates of O₂ consumption and CO₂ production are dependent on the metabolic rate of the body tissues. The inputs are the arterial O₂ and CO₂ concentrations, C_{aO₂} and C_{aCO₂}. The outputs are the venous O₂ and CO₂ concentrations, C_{vO₂} and C_{vCO₂}.

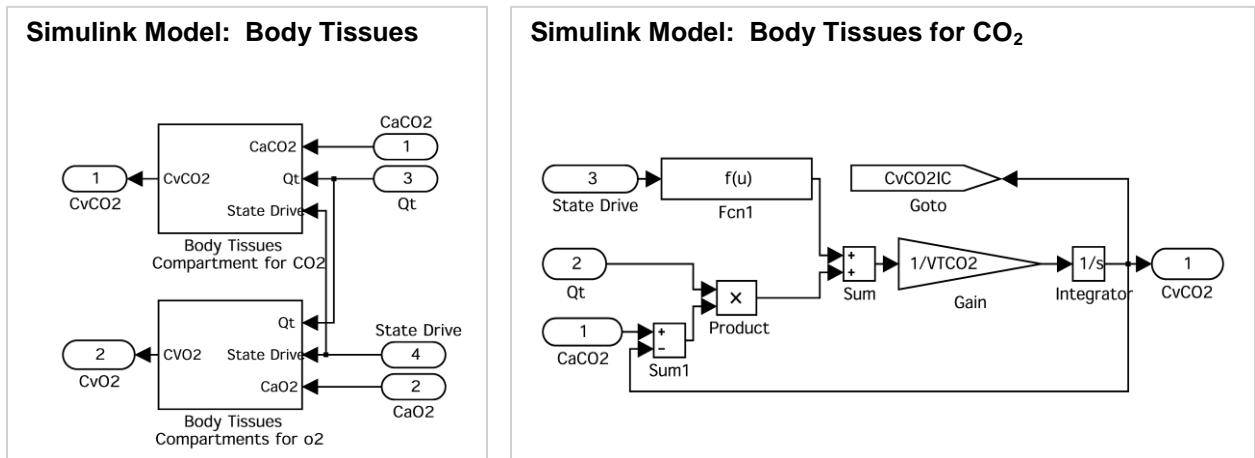


Body Tissues Equations:

$$\dot{Vt}_{CO_2} \dot{Cv}_{CO_2} = [MR_{CO_2} + \dot{Q}(C_{aCO_2} - Cv_{CO_2})]$$

$$\dot{Vt}_{O_2} \dot{Cv}_{O_2} = [-MR_{O_2} + \dot{Q}(C_{aO_2} - Cv_{O_2})]$$

Reference: Khoo, M.C.K., A model-based evaluation of the single-breath CO₂ ventilatory response test. *Journal of Applied Physiology*, 68(1):393-399, 1990.



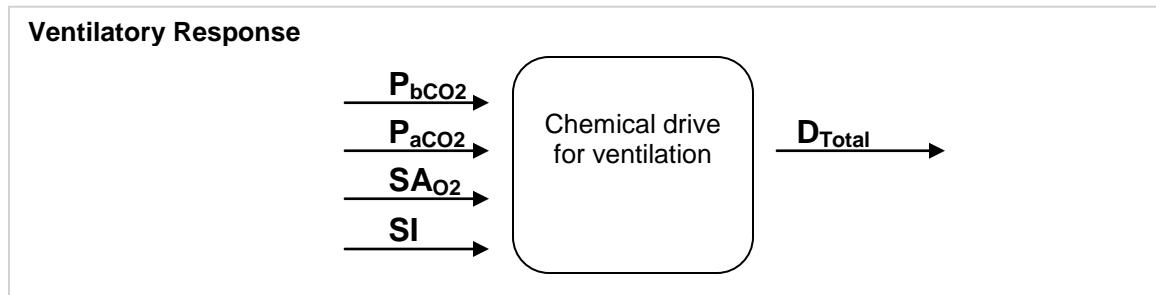
Note: O₂ compartment is the same as CO₂ compartment

Inputs:	C_{AO2}	Arterial O ₂ concentration
	C_{ACO2}	Alveolar CO ₂ partial pressure
Outputs:	C_{vCO2}	Arterial CO ₂ partial pressure
	C_{vO2}	Oxygen Saturation
Variables:	V_{tco2}	Body tissue storage volume for CO ₂
	V_{to2}	Body tissue storage volume for O ₂
	MR_{co2}	Metabolic production rate for CO ₂
	MR_{o2}	Metabolic consumption rate for O ₂
	$C_{vco2}IC$	Initial condition for mixed venous CO ₂ concentration
	$C_{vo2}IC$	Initial condition for mixed venous O ₂ concentration

Ventilatory Response (Vent_Drive_Khoo.mdl)

Description

The chemical driven ventilatory response is determined from the central and the peripheral chemoresponses during sleep-wake state. The central response is driven primarily by CO₂ while the peripheral response is modulated both by oxygen and carbon dioxide. The inputs for this compartment are the brain CO₂ partial pressure, P_{bCO₂}, arterial CO₂ partial pressure, P_{aCO₂} and oxygen saturation, SA_{O₂}. The output is the chemical drive for ventilation, D_{chem}.



Ventilatory Response Equations:

(a) For normal breathing,

$$D_{Total} = \begin{cases} Y, & TH_L \leq Y \leq TH_H \\ 0, & OW \end{cases}$$

$$Y = X / 2 + X / 2 \otimes [z_{p0} \cdot e^{-z_{p0} \cdot t} \cdot u(t)]$$

$$X = \begin{cases} 2 / (1 + e^{-5D_{Total_O}}) - 1, & D_{Total_O} > 0 \\ 0, & D_{Total_O} \leq 0 \end{cases}$$

(b) For sleep-disordered breathing,

$$D_{Total} = D_{Total_O}$$

where

$$D_{Total_O} = (1 - 0.4 \cdot SI) \cdot (D_{vent} - D_{state})$$

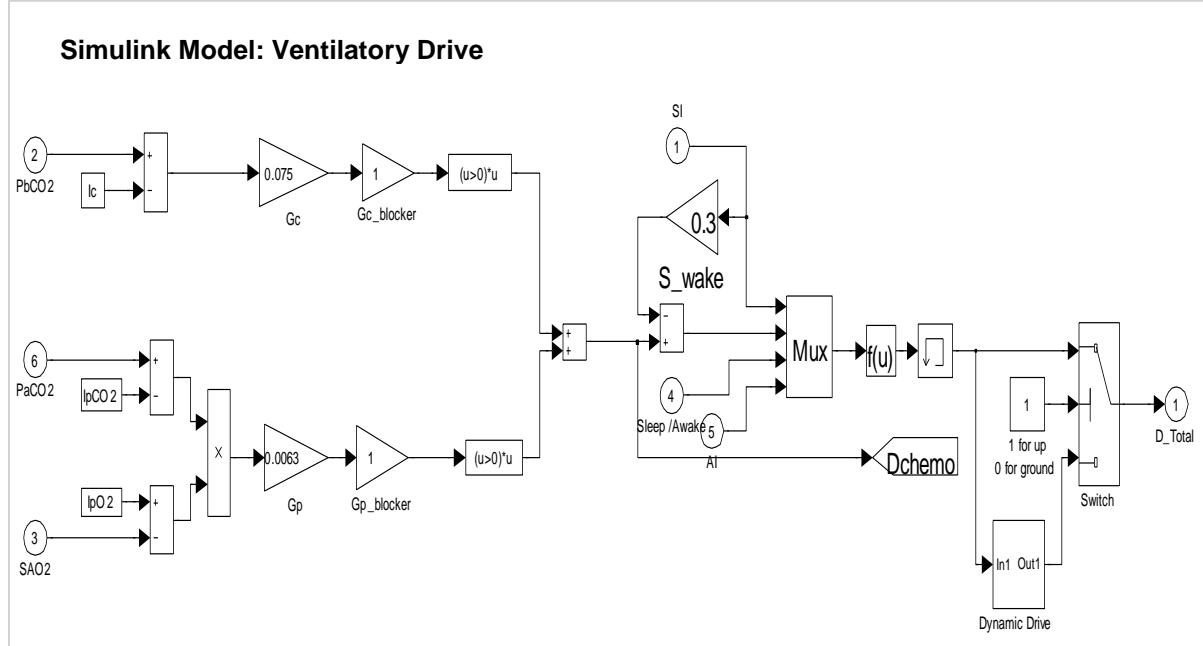
$$D_{state} = SI \cdot S_{wake}$$

$$D_{vent} = D_c + D_p$$

$$D_c = \begin{cases} G_c(P_{bCO_2} - I_c), & P_{bCO_2} > I_c \\ 0, & Otherwise \end{cases}$$

$$D_p = \begin{cases} G_p(P_{aCO_2} - I_{pCO_2}) \cdot (I_{pO_2} - SAO2), & P_{aCO_2} > I_{pCO_2} \& I_{pO_2} > SAO2 \\ 0, & Otherwise \end{cases}$$

Reference: Khoo, M.C.K., A model-based evaluation of the single-breath CO₂ ventilatory response test. *Journal of Applied Physiology*, 68(1):393-399, 1990.

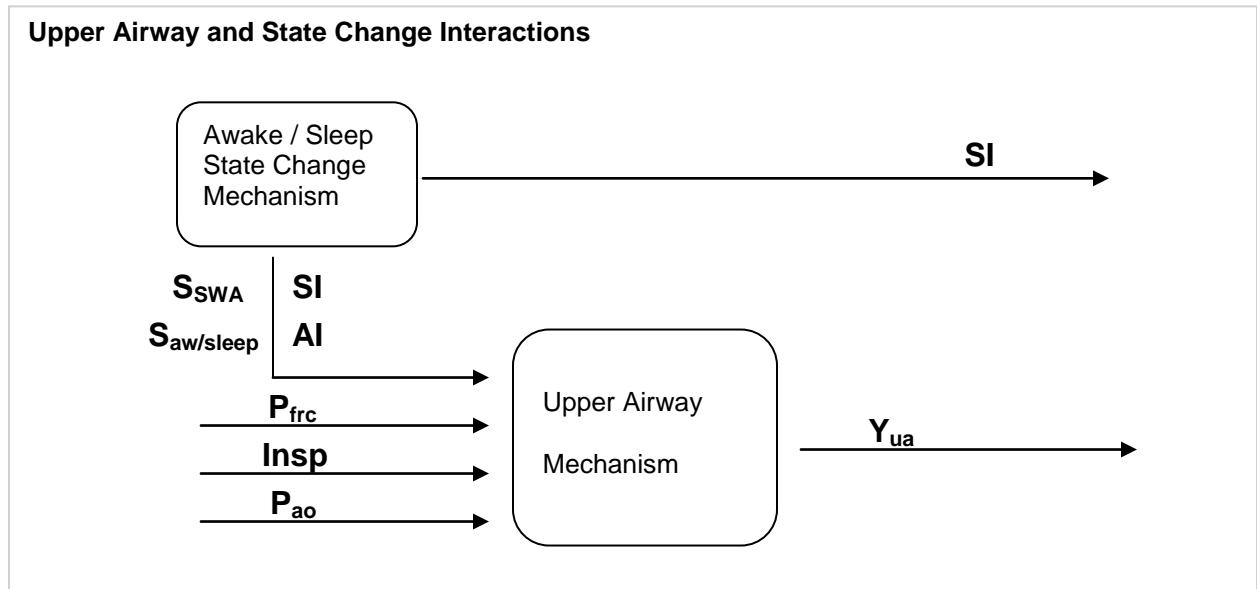


Inputs:	P_bCO₂	Brain CO ₂ partial pressure
	P_aCO₂	Arterial CO ₂ partial pressure
	SAO₂	Oxygen saturation
	SI	Sleep-wake state index
Output:	D_{Total}	chemical drive for ventilation
Variables:	I_c	Central apneic threshold
	I_pCO₂	Peripheral apneic threshold for CO ₂
	I_pO₂	Peripheral apneic threshold for O ₂
	G_c	Gain for central chemical drive
	G_p	Gain for peripheral chemical drive
	S_{wake}	Factor of wakefulness to sleep

Upper Airway / State Change (State_UA_Khoo_Borbely.mdl)

Description

Upper airway muscle tone decreases from wakefulness to sleep. This introduces the possibility of upper airway collapse under certain conditions. The simple model of upper airway mechanics employed here assumes that upper airway conductance (= reciprocal of resistance) is directly proportional to the "wakefulness" (or state-related ventilatory) drive.



Upper Airway

Description

Upper airway model is driven by pleural pressure, P_{pl} , total respiratory flow, Q_{total} in the airways, lower airway resistance, R_{la} and sleep-wakefulness state drive, SD . During the obstruction, the upper airway is narrowed, therefore the upper airway resistance to the airflow increases. Because the upper airway is entirely blocked during full obstruction, and its resistance becomes infinitely large, for modeling purposes we prefer to use the upper airway conductance, Y_{ua} which is the inverse of resistance. We model upper airway conductance as a function of upper airway opening surface area, A . It is a known fact that in patients with Obstructive Sleep Apnea the upper airway muscle tone is reduced and more prone to collapse. Therefore, the upper airway opening surface area depends on the airway pressure and upper airway compliance, C_{ua} that is in turn a function of upper airway sensitivity, s_{ua} and also depends on the sleep-wakefulness state drive SD . The upper airway muscle tone is represented by the upper airway sensitivity. In wakefulness, the sensitivity remains low, but with the sleep onset the sensitivity increases. The net effect is to impose an additional load on respiratory effort.

All these mechanisms are inter-dependent on each other and connected to lower respiratory airways as well in a closed loop mode.

Upper Airway Equations:

$$(P_{ao} - P_{ua}) \cdot Y_{ua} = \dot{V} - \dot{V}_{ua}$$

where $Y_{ua} = I / R_{ua}$

$$P_{ua} = -\frac{P_{crit}(SI)}{b_{ua}} \int V_{ua} dt - V_{ua} \cdot R_{uaw}$$

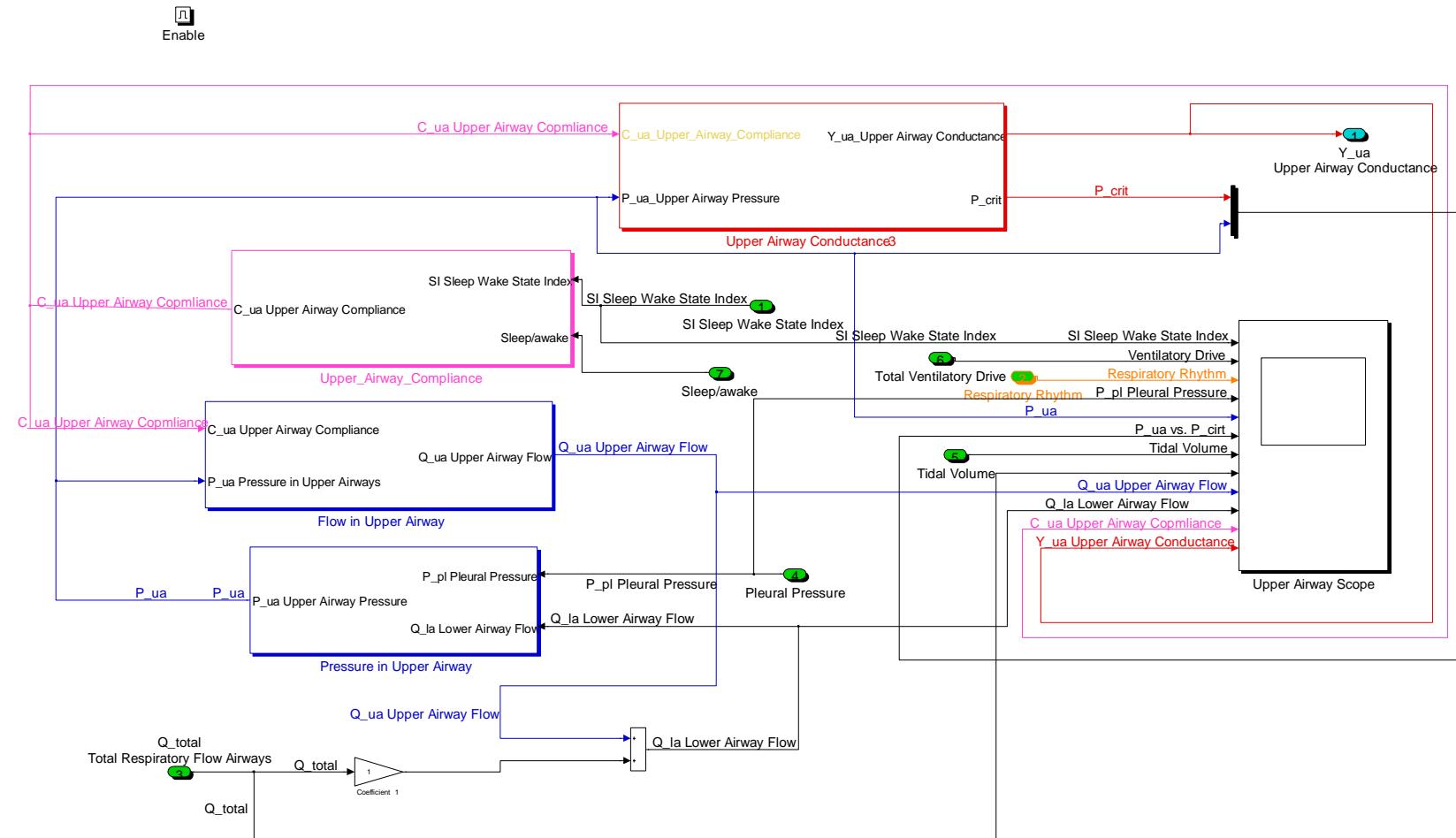
$$Y_{ua}(SI) = k_{ua} \cdot A_{ua}, \text{ where } A_{ua} = \begin{cases} 0, & P_{ua} \leq P_{crit} \\ A_{0ua} \cdot (1 - P_{ua} / P_{crit}(SI)), & P_{crit} < P_{ua} \leq 0 \\ A_{0ua}, & P_{ua} > 0 \end{cases}$$

$$P_{crit}(SI) = \begin{cases} P_{crit_awake}, & SI = 0 \text{ (awake)} \\ P_{crit_awake} / (1 + S_{ua} \cdot (SI)^2) / (1 - Sleepawake), & 0 < SI < 1, \\ P_{crit_awake} / (1 + S_{ua}), & SI = 1 \text{ (sleep)} \end{cases}$$

(A.40)

where $Sleepawake$ is 0 during sleep and 1 during wakefulness, S_{ua} is upper airway sensitivity and is directly related to P_{crit} .

Simulink Model: Upper Airway Mechanism



Inputs:	SI	Sleep-wake State Drive
	P_{pl}	Pleural Pressure
	Q_{total}	Total Respiratory Flow
	R_{la}	Lower Airway Resistance
	Sleep/Awake	Sleep or Awake state
	D_{Total}	Total ventilatory drive
	V_t	Tidal volume
	Resp_Rhm	Respiratory rhythm
Outputs:	Y_{ua}	Upper Airway Conductance
Variable:	S_{ua}	Upper Airway sensitivity
	R_{uaw}	Upper airway wall resistance
	A_{0ua}	Maximum area of opening in upper airway
	K_{ua}	Proportionality coefficient between A _{ua} and Y _{ua} ;
	P_{crit_awake}	Critical upper airway pressure in wakefulness
	C_{ua}	Upper airway compliance
	P_{ua}	Upper airway pressure
	\dot{V}_{ua}	Upper airway flow
	\dot{V}	Total flow in airways

Sleep Mechanism

In the sleep mechanism model, the awake/sleep state is determined by a combination of the circadian rhythm and a sleep propensity index that is correlated with slow wave activity. The upper circadian threshold marks the point at which sleep onset occurs, while the lower limit triggers awakening. The circadian rhythm is modeled as a skewed sine function. The NREM and REM stages during sleep are determined by the slow wave activity with no activity in REM stage and an overall decaying throughout the night for the NREM stage. The input for this compartment is the total ventilatory drive, **D_{vent}**. The outputs are state drive, **SI**, awake/sleep state change, **S_{aw/sleep}**, sleep stage, **S_{SWA}** and arousal, **D_{arousal}**.

Sleep Mechanism Equations:

Process C:

$$C_{H/L} = A[0.97 \sin \theta + 0.22 \sin(2\theta) + 0.07 \sin(3\theta) + 0.03 \sin(4\theta) + 0.001 \sin(5\theta)] + X$$

where $A = 0.12$, $X = X_H = 0.9$ for C_H , $X = X_L = 0.15$ for C_L .

Process S:

$$\text{Awake State } (S \geq C_L): S(t) = 1 - [1 - S(t - \Delta t)]e^{(-0.055\Delta t / 3600)}$$

$$\text{Sleep State } (S \leq C_H): \frac{dS}{dt} = -\alpha_{gc} \cdot SWA$$

$$\frac{dSWA}{dt} = \alpha_{rc} \cdot SWA \left(1 - \frac{SWA}{S}\right) - \alpha_{fc} \cdot SWA \cdot REMT(t) + SWA \cdot n(t)$$

$$REMT(t) = REM + 0.2 \cdot AI$$

$$REM = \begin{cases} 1 & \text{REM} \\ 0 & \text{NREM} \end{cases}$$

$$AI = \begin{cases} 1, & D_{\text{Total}} > \text{Thre} \\ 0, & \text{Otherwise} \end{cases}, \text{ where Thre} = I_{\text{vent}} (0.7 + 0.3 S_{SWA})$$

$$S_{SWA} = 1.2 \cdot \frac{SWA}{S}$$

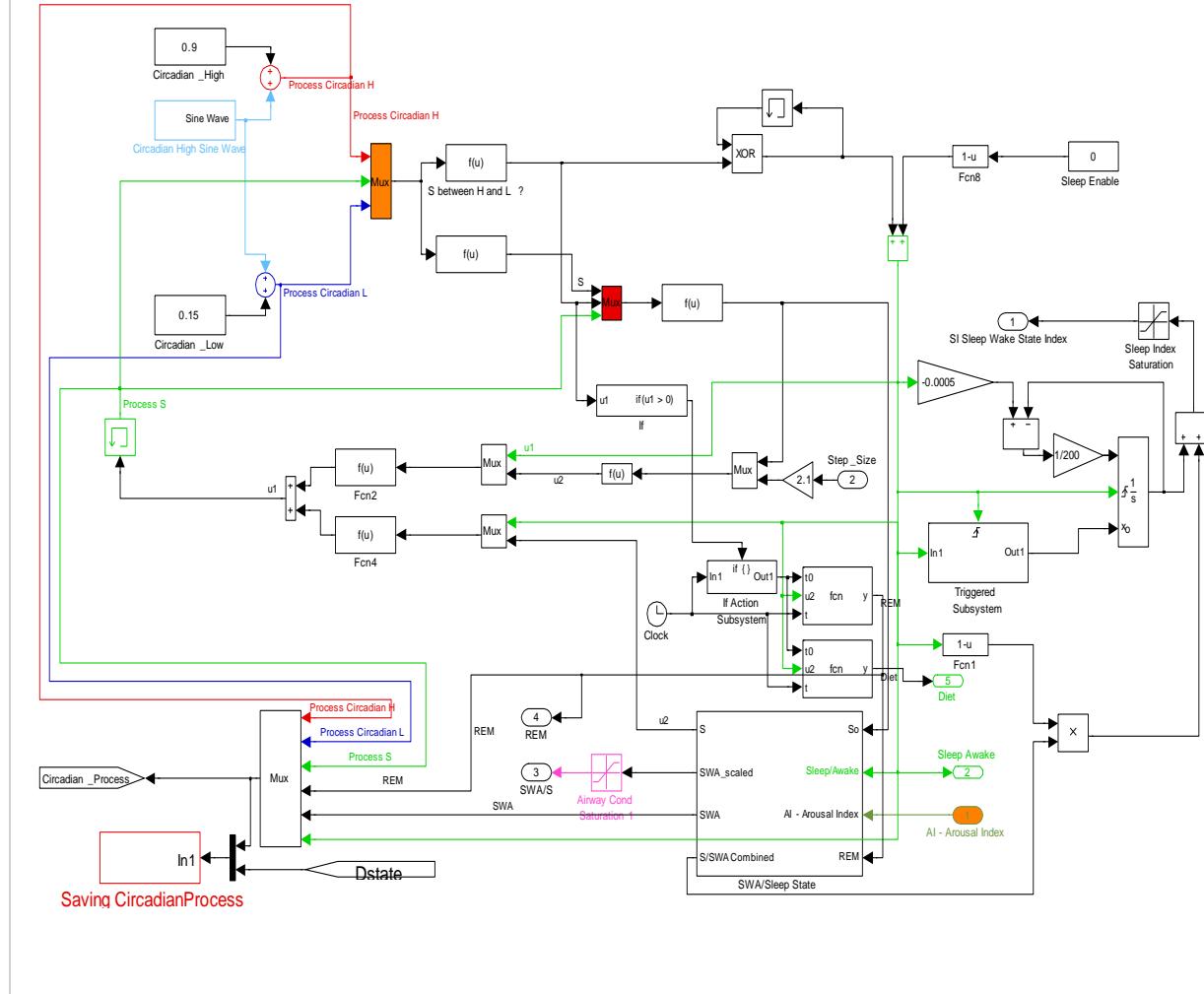
$$D_{state} = SI = \begin{cases} S_{SWA}, & \text{sleep onset transition} \\ S_{SWAcombined}, & \text{sleep} \\ 0, & \text{awake} \end{cases}$$

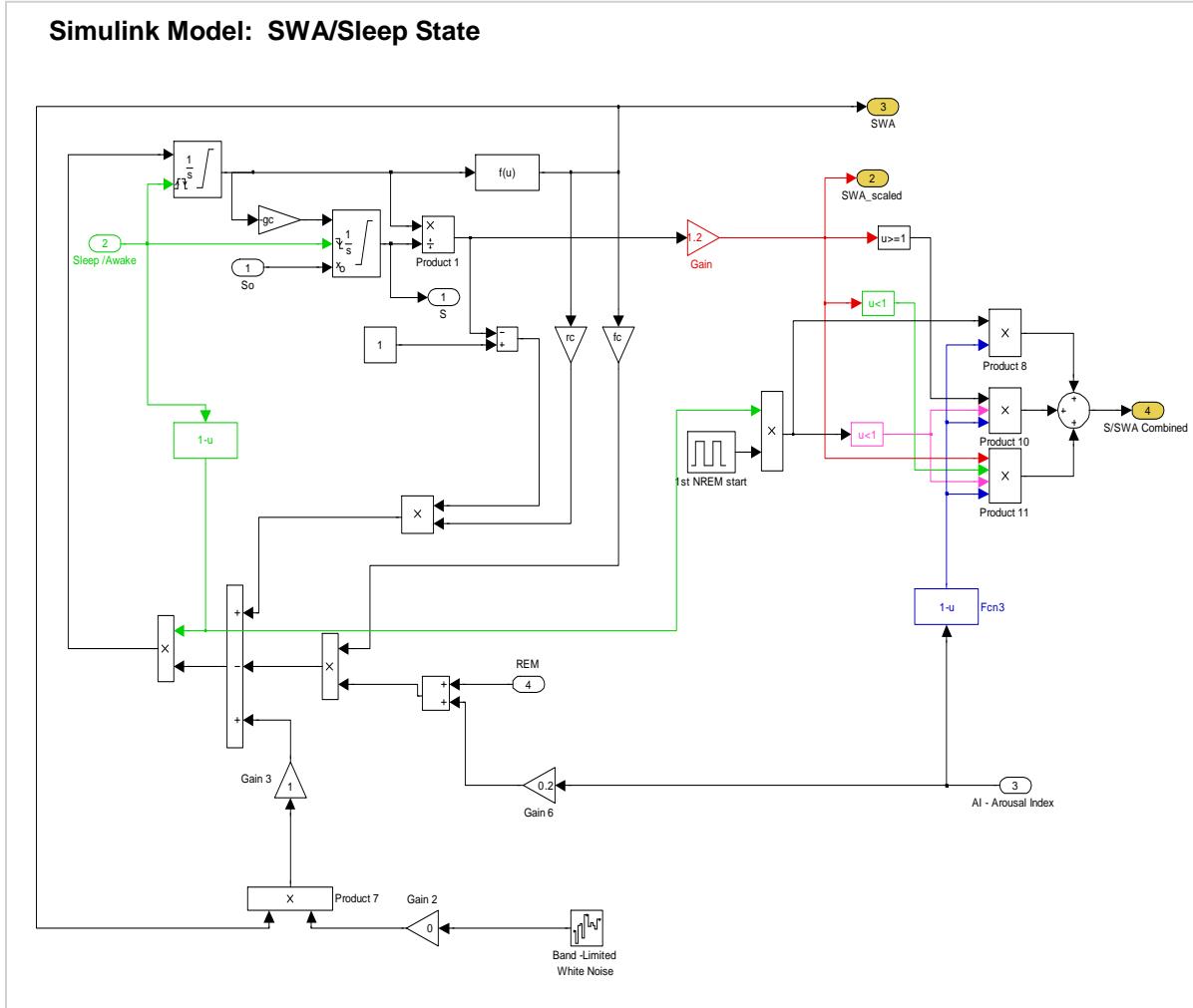
$$S_{SWAcombined} = \begin{cases} 1, & AI = 0 \\ 0, & AI = 1 \end{cases}$$

Reference: Khoo, M.C.K. A model-based evaluation of the single-breath CO₂ ventilatory response test. *Journal of Applied Physiology*, 68(1):393-399, 1990.

Achermann, P., Borbely, A.A. Mathematical models of sleep regulation. *Frontiers in Bioscience*, 8, s683-693, 2003.

Simulink Model: Sleep Mechanism



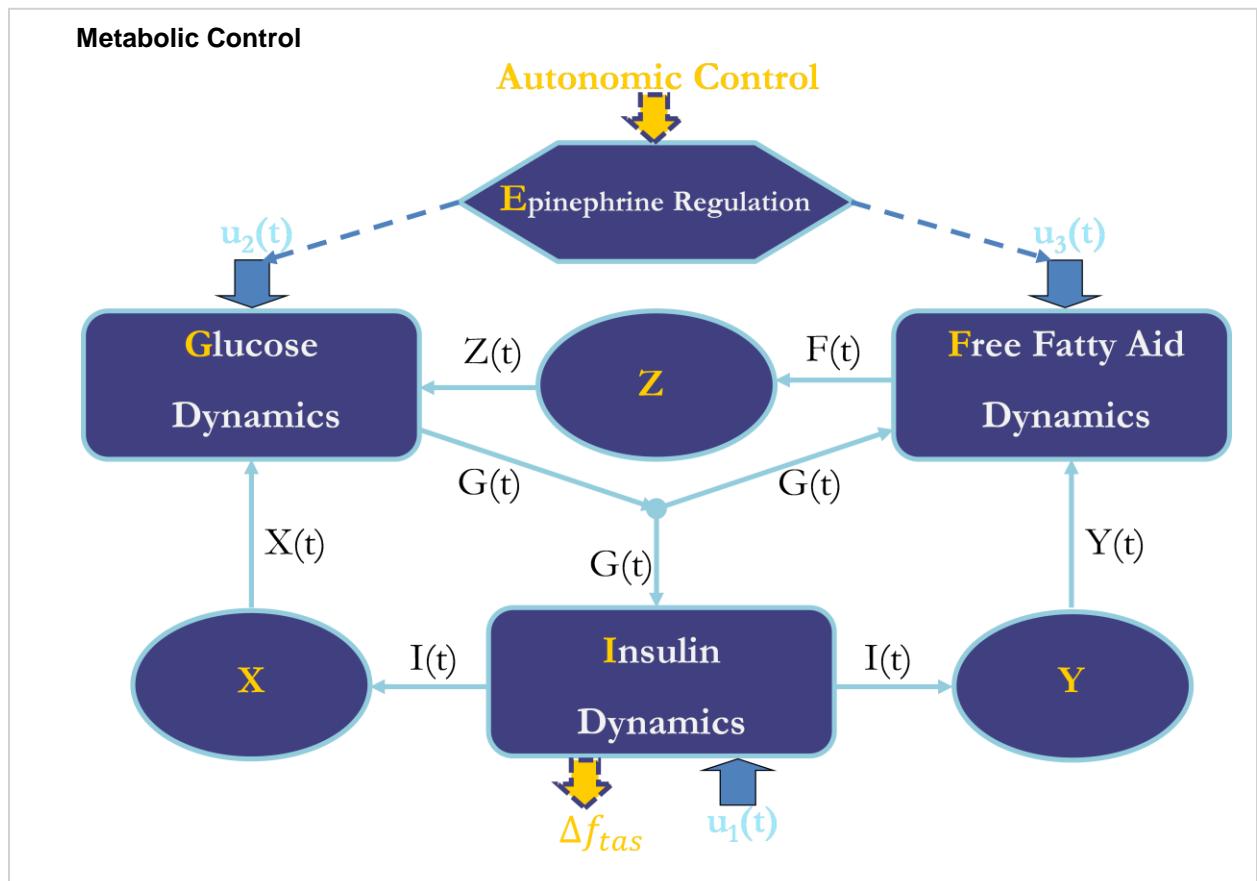


Inputs:	D_{vent}	Total Ventilatory Drive
Outputs:	D_{arousal}	Arousal State
	D_{state}	State Drive
	S_{aw/sleep}	Awake/Sleep State change
	S_{SWA}	Sleep Stage
Variables:	A	Amplitude of the skewed sine function
	X_H	Bias of the skewed sine function for process CH
	X_L	Bias of the skewed sine function for process CL
	α_{gc}	Constant for sleep decaying
	α_{rc}	Rising rate of slow wave activity
	α_{fc}	Falling rate of slow wave activity
	SWAo	Initial value of sleep wake activity

Metabolic Control (PNEUMA.mdl)

Description

The metabolic control include the circadian regulation of epinephrine secretion, epinephrine regulation on dynamic fluctuations in glucose and free-fatty acid in plasma, metabolic coupling among tissues and organs provided by insulin and epinephrine, as well as the effect of insulin on peripheral vascular sympathetic activity. The inputs for this compartment are the alpha-sympathetic activity, $f_{tas,res}$, sleep state index, **SI**, REM sleep, **REM**, and diet uptake, **DIET**. The output is the change in the α -sympathetic response, Δf_{tas} .



Metabolic Control Equations:

Glucose Insulin and Free-fatty Acid Dynamics:

$$\frac{dG(t)}{dt} = -p_1 G(t) + p_1 G_b - p_4 X(t)G(t) + p_4 X_b G_b + p_6 Z(t)G(t) - p_6 G_b Z_b + \frac{k_{EG} u_{2int}(t) + u_{2ext}(t)}{Vol_G}$$

$$\begin{aligned}
\frac{dI(t)}{dt} &= \gamma(G(t-T_{Di}) - G_h)t - n(I(t) - I_b) + p_5u_1(t) \\
\frac{dX(t)}{dt} &= -p_2(X(t) - X_b) + p_3(I(t) - I_b) \\
\frac{dY(t)}{dt} &= -p_{F2}(Y(t) - Y_b) + p_{F3}(I(t) - I_b) \\
\frac{dF(t)}{dt} &= -p_7F(t) + p_7F_b - p_8Y(t)F(t) + p_8Y_bF_b + p_9^G G(t)F(t) - p_9^G G_bF_b + \frac{k_{EF}u_{3int}(t) + u_{3ext}(t)}{Vol_F} \\
\frac{dZ(t)}{dt} &= -k_2(Z(t) - Z_b) + k_1(F(t) - F_b)
\end{aligned}$$

where $p_9^G = 0.00021e^{-0.0055G}$

Epinephrine Regulation:

$$V_{x,i} = V_{x,i}^o \left(1.0 + \lambda_{x,i}^E \frac{(\Delta \cdot E(t) - E(0))^2}{\alpha_{x,i}^E + (\Delta \cdot E(t) - E(0))^2} \right)$$

where subscript x = “heart”, “muscle”, “gastrointestinal tract”, “adipose tissue” or “other tissues”; subscript i = “glucose” (assuming the metabolic pathway: GLC \leftrightarrow G6P \leftarrow GLY) or “FFA” (assuming the metabolic pathway: TGL \leftrightarrow FFA \rightarrow ACoA).

$$u_{2int}(t) = \sum_x V_{x,i}(t)$$

$$u_{3int}(t) = \sum_x V_{x,i}(t)$$

$$E(t) = E(0) + E_b \cdot \omega(f_{tas,meta}) \cdot [1.0 - \exp(-t/\tau_E)]$$

Autonomic and Metabolic Interactions (Forward Pathway):

$$\omega(f_{tas,meta}) = [f_{tas,meta} - f_{tas,meta0} + 1]^{-SI \cdot G_{as_sleep}} \cdot (1 + b_{REM} \cdot REM) \cdot (1 - SI \cdot a_\omega)$$

$$f_{tas,meta} = f_{tas} \cdot (1 - SI \cdot G_{as_sleep})$$

$$f_{tas,meta0} = f_{tas,0} (1 - SI \cdot G_{as_sleep})$$

$$E(0) = E_b + K_{Ce,0} \cdot (f_{tas,meta} - f_{tas,meta0}) \cdot (1 - SI)$$

Autonomic and Metabolic Interactions (Feedback Pathway):

$$W(I) = k_{as} + k_{as} \cdot f_{tas,I0} \cdot \frac{\exp[(I - I_b)/k_{isc,I}] - 1}{\exp[(I - I_b)/k_{isc,I}] + 1}$$

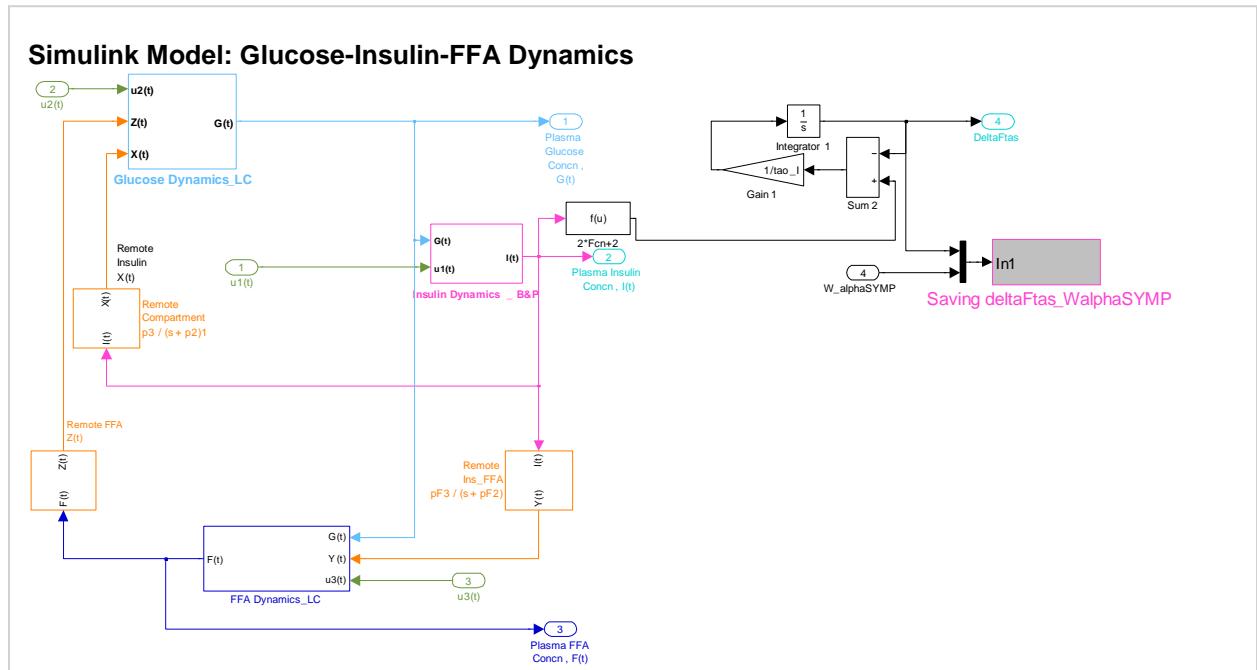
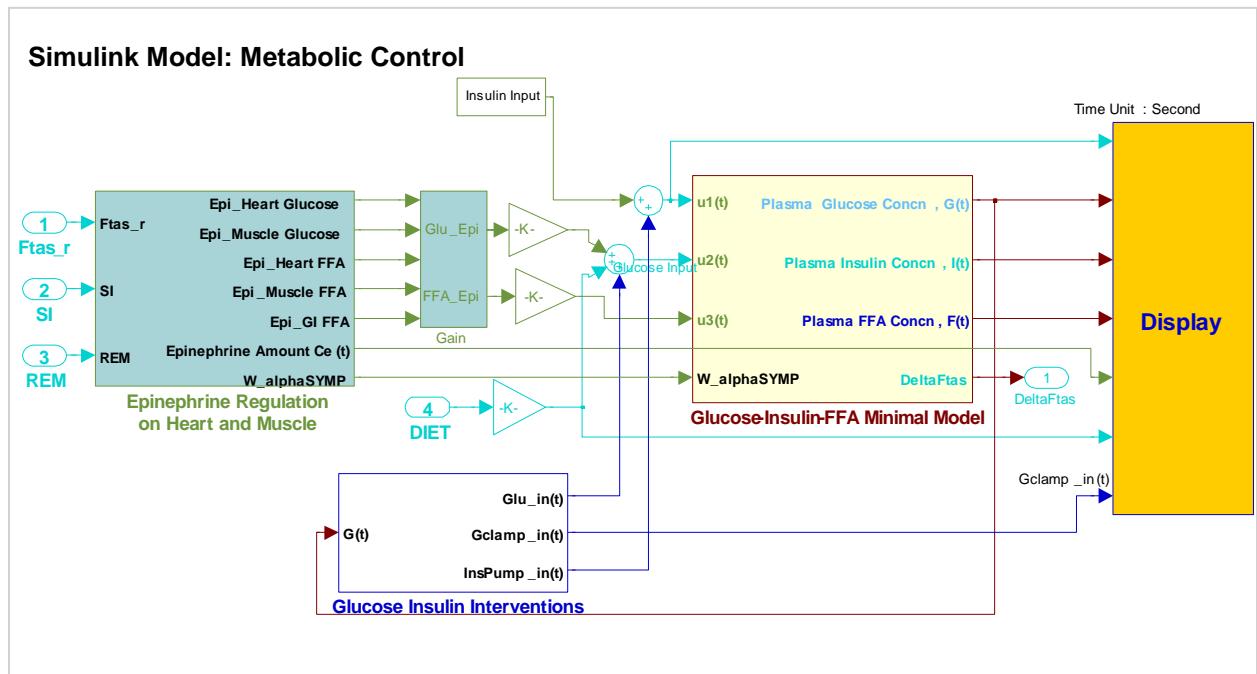
$$\Delta f_{tas} = W(I) \cdot [1 - \exp(-t/\tau_I)]$$

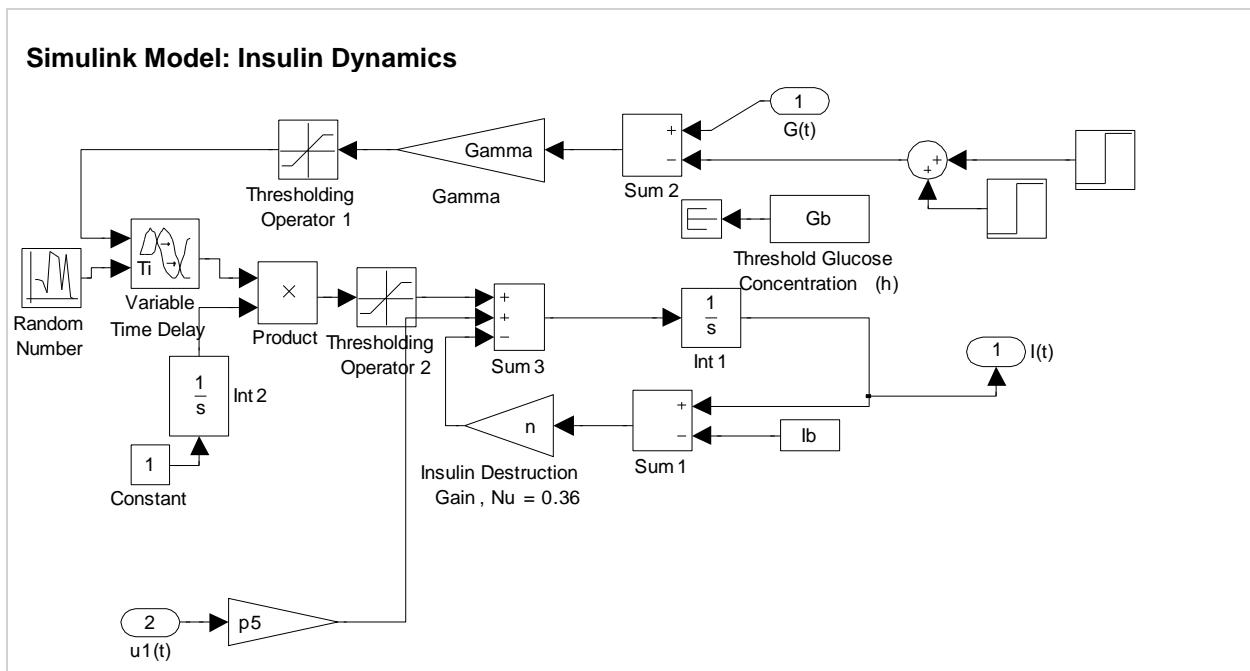
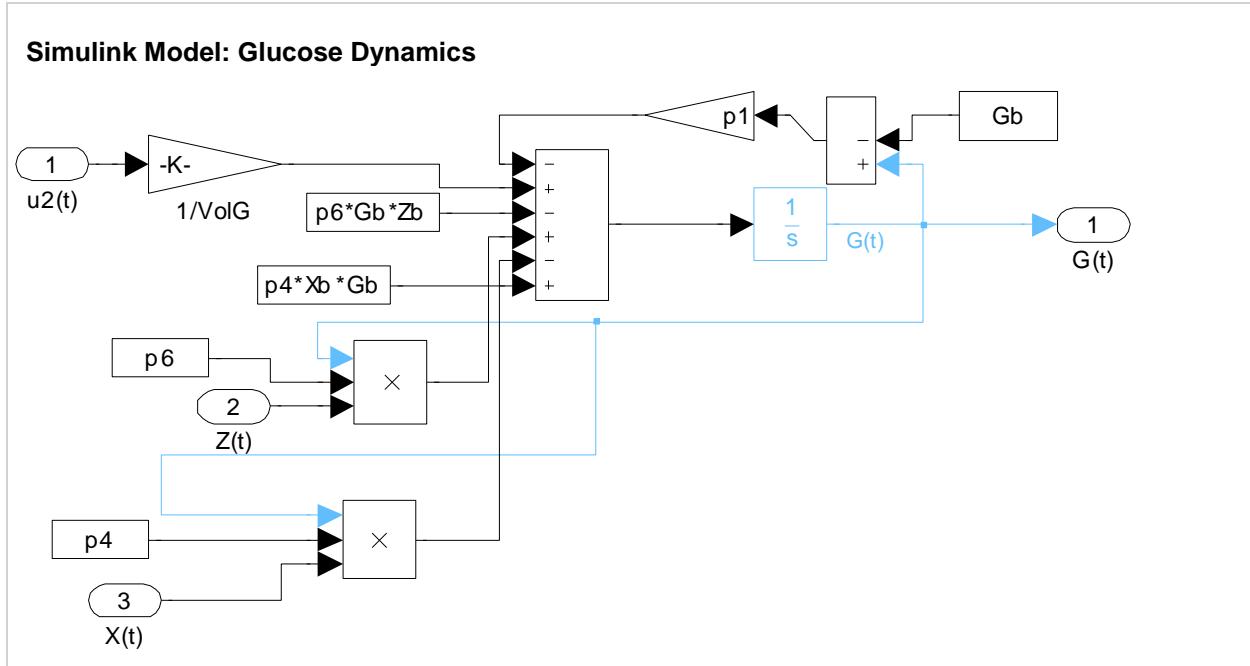
$$f_{tas,FB} = f_{tas} + \Delta f_{tas}$$

where $f_{tas} = f_{tas,res}$ and $f_{tas,vein}$, respectively.

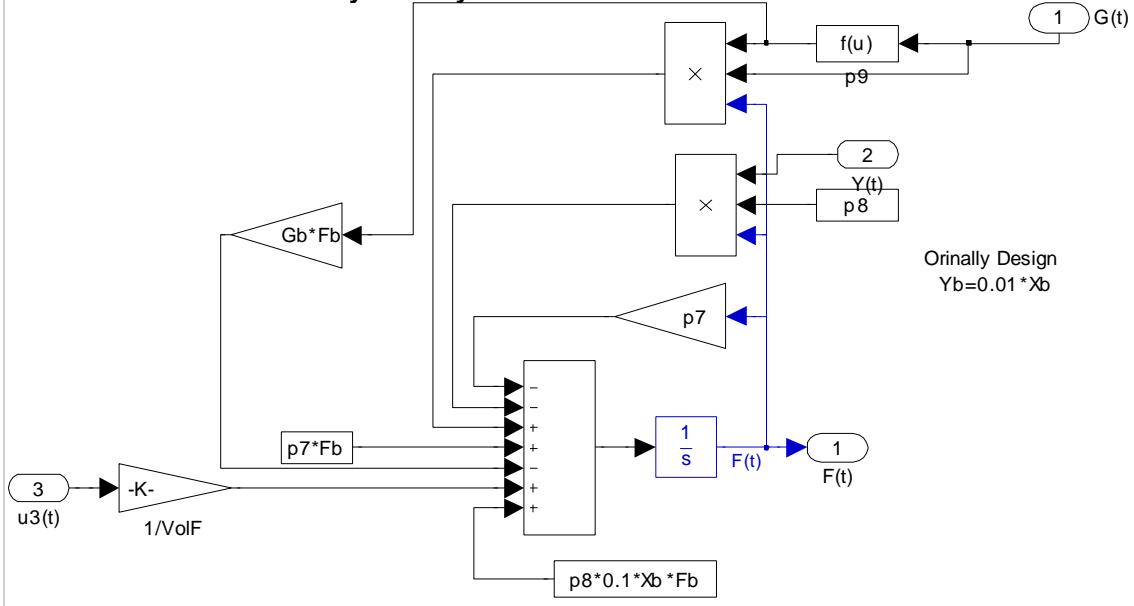
Reference:

1. Kim, J., Saidel, G. M., and Cabrera, M. E. Multi-scale computational model of fuel homeostasis during exercise: effect of hormonal control. *An Biomed Eng* 35(1): 69-90, 2006.
2. Roy, A., and Parker, R. S. Dynamic modeling of free fatty acid, glucose, and insulin: an extended “Minimal Model”. *Diabetes Tech Therapeu* 8(6): 617-626, 2006.

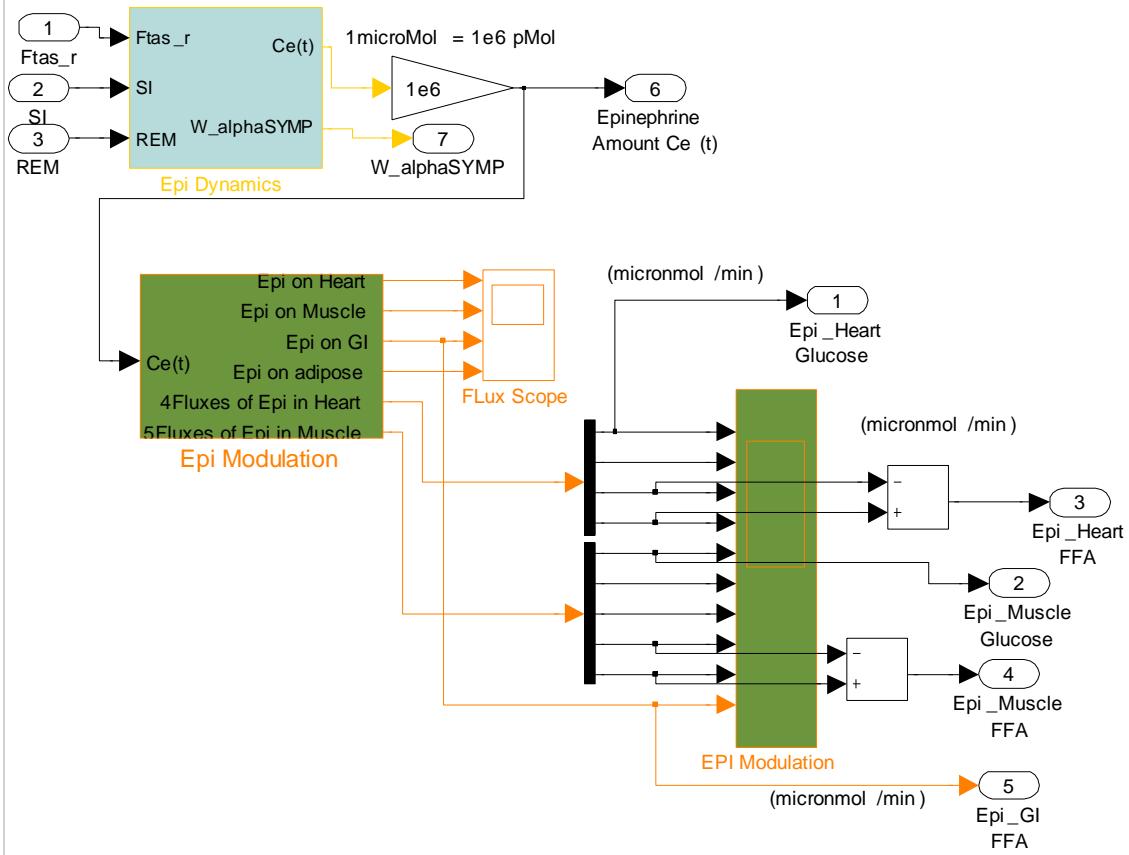




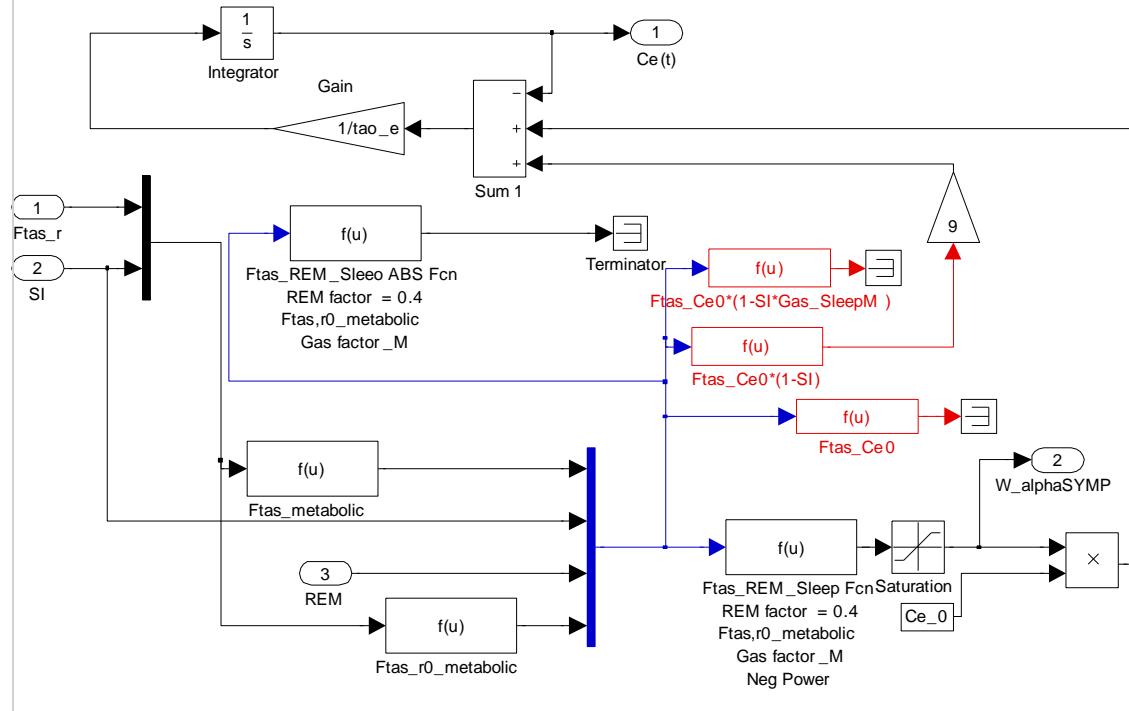
Simulink Model: Free-Fatty Acid Dynamics



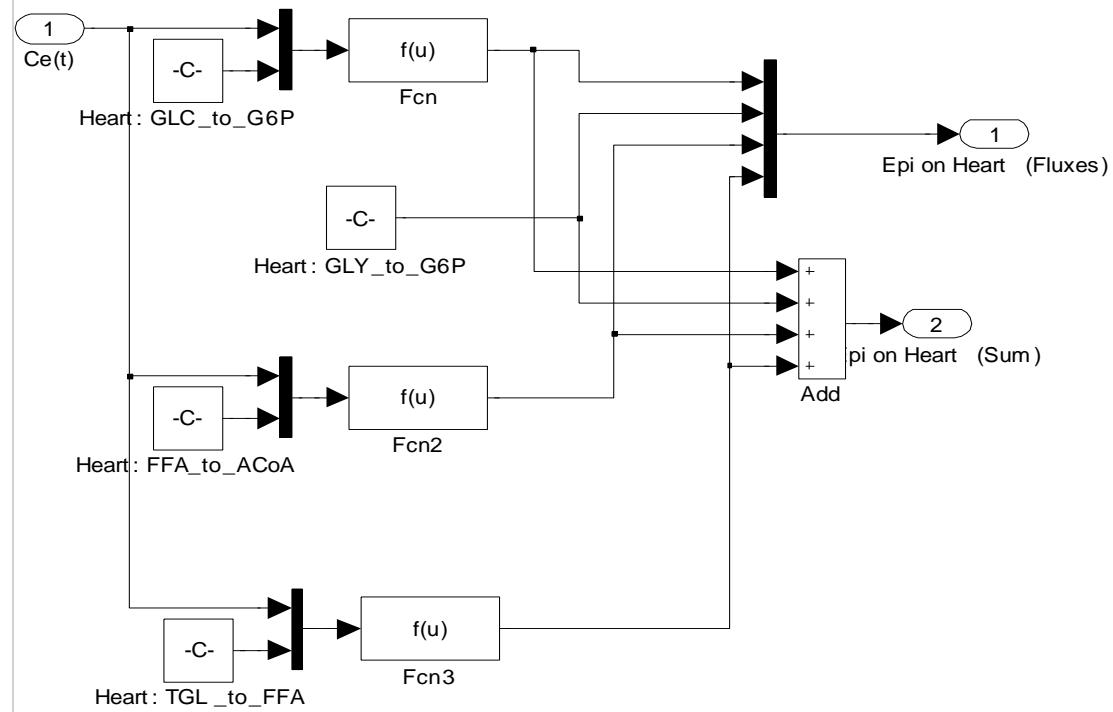
Simulink Model: Epinephrine Regulations

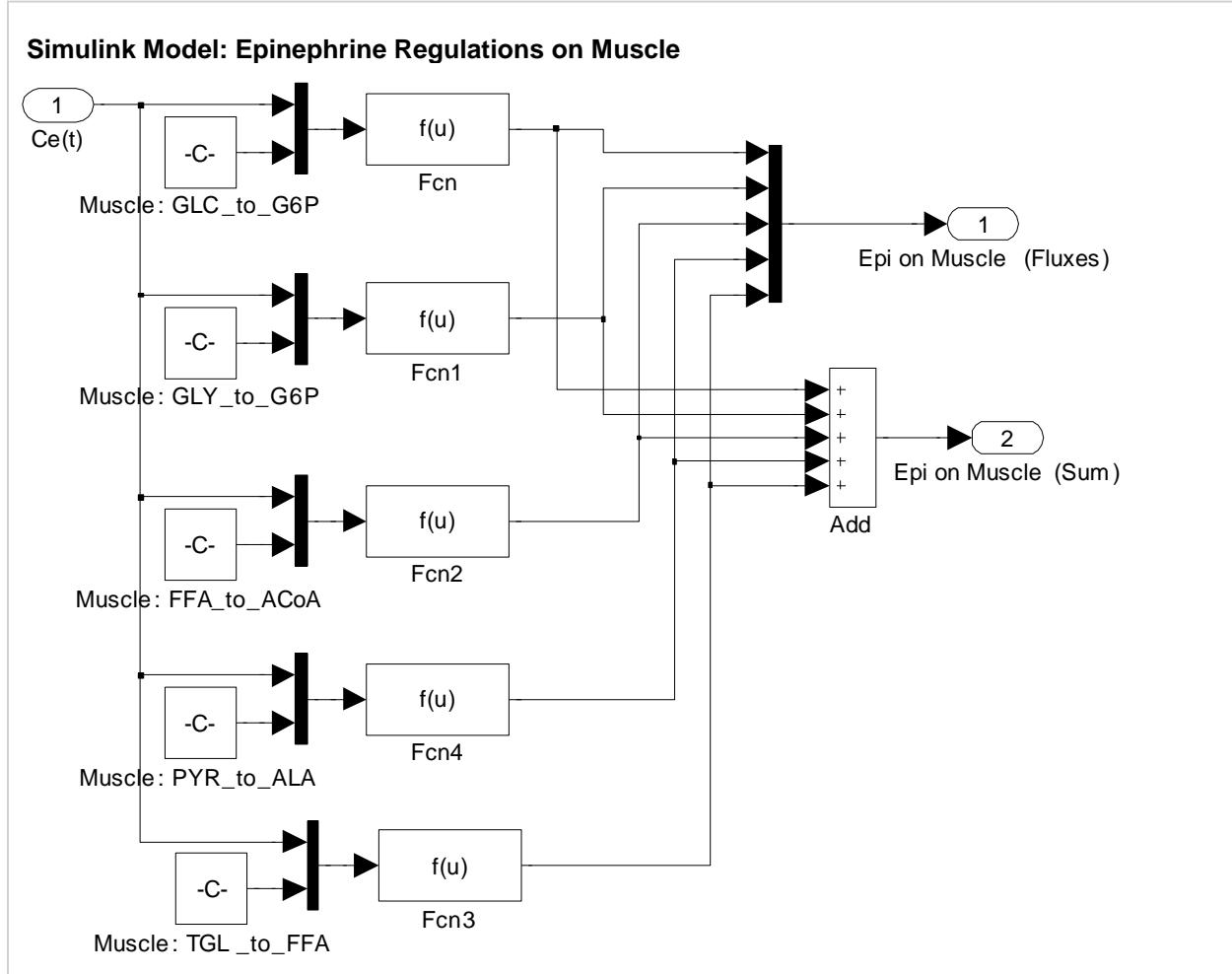


Simulink Model: Epinephrine Dynamics



Simulink Model: Epinephrine Regulations on Heart





Inputs:	$f_{tas,res}$	Alpha-sympathetic Response
	SI	Sleep State Index
	REM	REM Sleep Signal
	DIET	Diet Glucose Uptake
Outputs:	Δf_{tas}	Change in Alpha-sympathetic Response
Variables:	G	Plasma Glucose Concentration
	I	Plasma Insulin Concentration
	X	Remote Plasma Insulin Concentration
	Y	Remote Plasma Insulin Concentration that Promotes FFA Production
	F	Plasma FFA Concentration
	Z	Remote Plasma FFA Concentration
	E	Epinephrine Concentration In Plasma

Autonomic and Metabolic Interactions

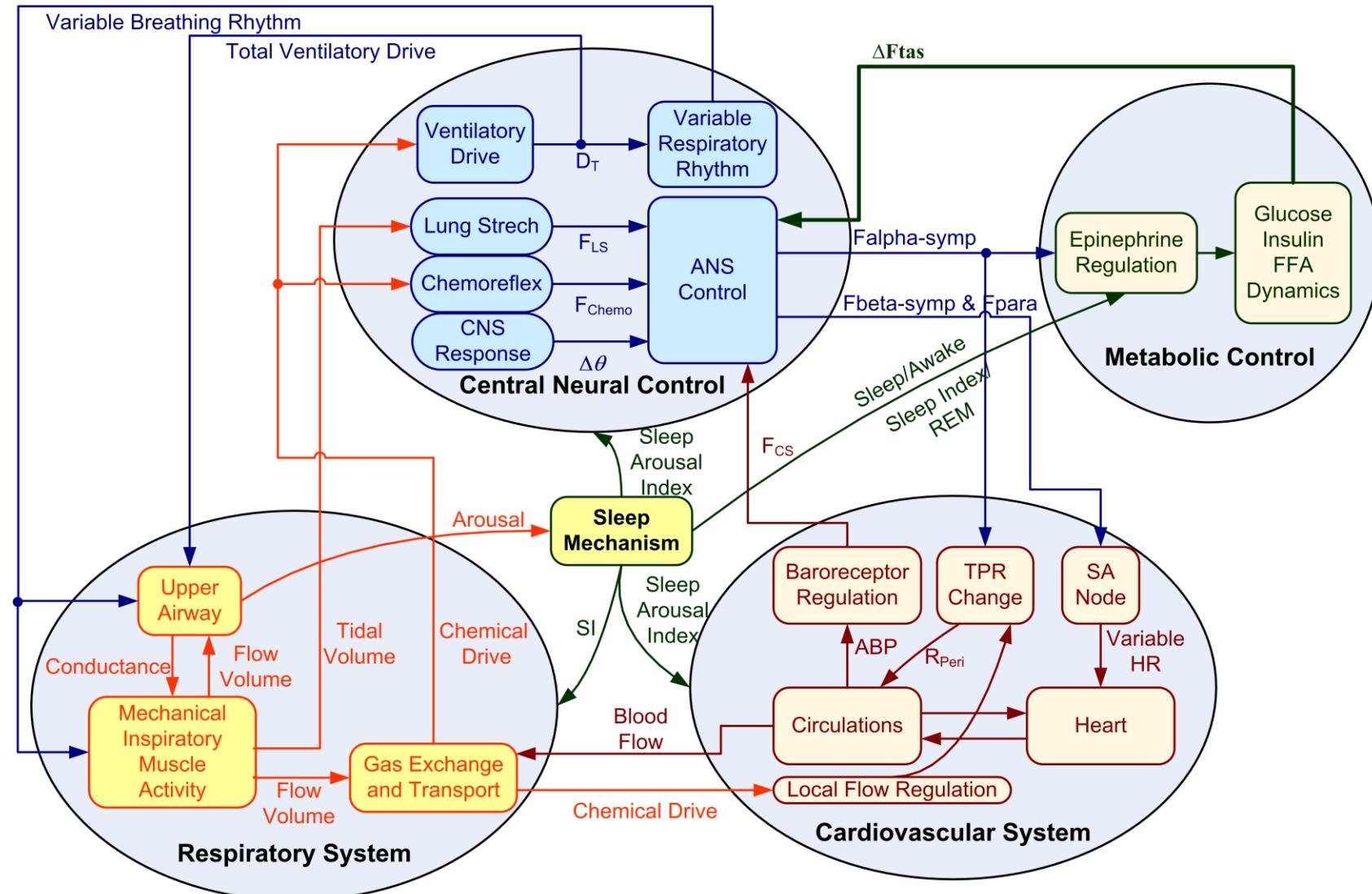
Description

PNEUMA is extended from previous Version 2.0, an existing integrative model of respiratory, cardiovascular and sleep-wake state control, to incorporate a sub-model of glucose-insulin-fatty acid regulation. This computational model is capable of simulating the complex dynamics of cardiorespiratory control, chemoreflex and state-related control of breath-to-breath ventilation, state-related and chemoreflex control of upper airway potency, respiratory and circulatory mechanics, as well as the metabolic control of glucose insulin dynamics and its interactions with the autonomic control.

The interactions between autonomic and metabolic control include the circadian regulation of epinephrine secretion, epinephrine regulation on dynamic fluctuations in glucose and free-fatty acid in plasma, metabolic coupling among tissues and organs provided by insulin and epinephrine, as well as the effect of insulin on peripheral vascular sympathetic activity.

These model simulations provide insight into the relative importance of the various mechanisms that determine the acute and chronic physiological effects of sleep-disordered breathing. The model can also be used to investigate the effects of a variety of interventions, such as different glucose clamps, the intravenous glucose tolerance test and the application of continuous positive airway pressure on obstructive sleep apnea subjects. incorporates several key cardiorespiratory reflexes and interactions. The schematic diagram below shows the overall scheme in which these interactions have been incorporated.

Scheme 1. Interactions of Autonomic Control and Metabolic Control

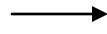


Appendix I: Software Package

Here are all the files for either the whole Pneuma or its individual modules. Please check to make sure that you have downloaded all those files you need.

Overall PNEUMA Package:

PneumaRelease3.zip



FILES

- PNEUMA.mdl
- pneuma_acc.dll
- PNEUMA_MAIN_CONTROL_PANEL.fig
- PNEUMA_MAIN_CONTROL_PANEL.m
- pneuma_variables.m
- pneuma_gains.m
- constant_parameters_6.fig
- constant_parameters_6.m
- adjustable_inputs_6.fig
- adjustable_inputs_6.m
- About.fig
- About.m
- directory_list.fig
- directory_list.m
- directory_list_load.m
- directory_list_load.fig
- directory_list_save.fig
- directory_list_save.m
- acquire_data.m
- acquire_data_save.m
- interventions.fig
- interventions.m
- cond_check.m
- release_note.pdf
- modaldlg.fig
- modaldlg.m
- CNS.bmp
- cpap2.bmp
- CV_pic.bmp
- IC_pic.bmp
- Metabolic2.bmp
- Respiratory_System.bmp
- PNEUMAResearch3_MANUAL.pdf

Individual Modules:

Cardiovascular System:

Cardiovascular



- Cardiovascular.mdl
- Cardiovascular_IC.m

Autonomic Control:

Autonomic → **Autonomic.mdl**
Autonomic_IC.m

SA Node:

SA_Ursino → **SA_Node_Ursino.mdl**
SA_Node_Ursino_IC.m

Total Peripheral Resistance change:

TPR_Ursino → **TPR_Ursino.mdl**
TPR_Ursino_IC.m

Respiratory System:

Respiratory System

Respiratory

→ **Respiratory.mdl**
Respiratory IC.m

NeuroMuscular Profile:

NeuroMuscular → **NeuroMuscular.mdl**
NeuroMuscular.JC.m

Respiratory Mechanics (whole):

Resp_Mech → **Resp_Mech.mdl**
Resp Mech IC.m

Respiratory Mechanics (Pmus):

Pmus_Flow_Younes → **Pmus_Flow_Younes.mdl**
Pmus_Flow_Younes_IC.m

Respiratory Mechanics (Pleural Pressure):

Pleural_Schulessler → **Pleural_Schulessler.mdl**
Pleural_Schulessler → **Pleural_Schulessler_IC.m**

State/Upper Airway Interaction:

State_UA_Khoo → **State_UA_Khoo.mdl**
State UA Khoo IC.m

Gas Exchange (Overall model):

Gas_Exchange → **Gas_Exchange.mdl**
Gas Exchange IC.m

Gas Exchange (Individual):

Dead_Space_Khoo → **Dead_Space_Khoo.mdl**
Dead_Space_Khoo_IC.m

Lungs Khoo

→ Lungs_Khoo.mdl
Lungs Khoo IC.m

Cardio Mix Lange

Cardio_Mix_Lange.mdl
Cardio Mix Lange IC.m

Dissociation Spencer

→ Dissociation_Spencer.mdl
Dissociation Spencer JC.m

Brain_Khoo	→	Brain_Khoo.mdl Brain_Khoo_IC.m
Body_Khoo	→	Body_Khoo.mdl Body_Khoo_IC.m
Vent_Drive_Khoo	→	Vent_Drive_Khoo.mdl Vent_Drive_Khoo_IC.m
Reflex_Ursino	→	Reflex_Ursino.mdl Reflex_Ursino.IC
State_UA_Khoo_Borbely	→	State_UA_Khoo_Borbely.mdl State_UA_Khoo_Borbely_IC

Appendix II: Saved Data Files

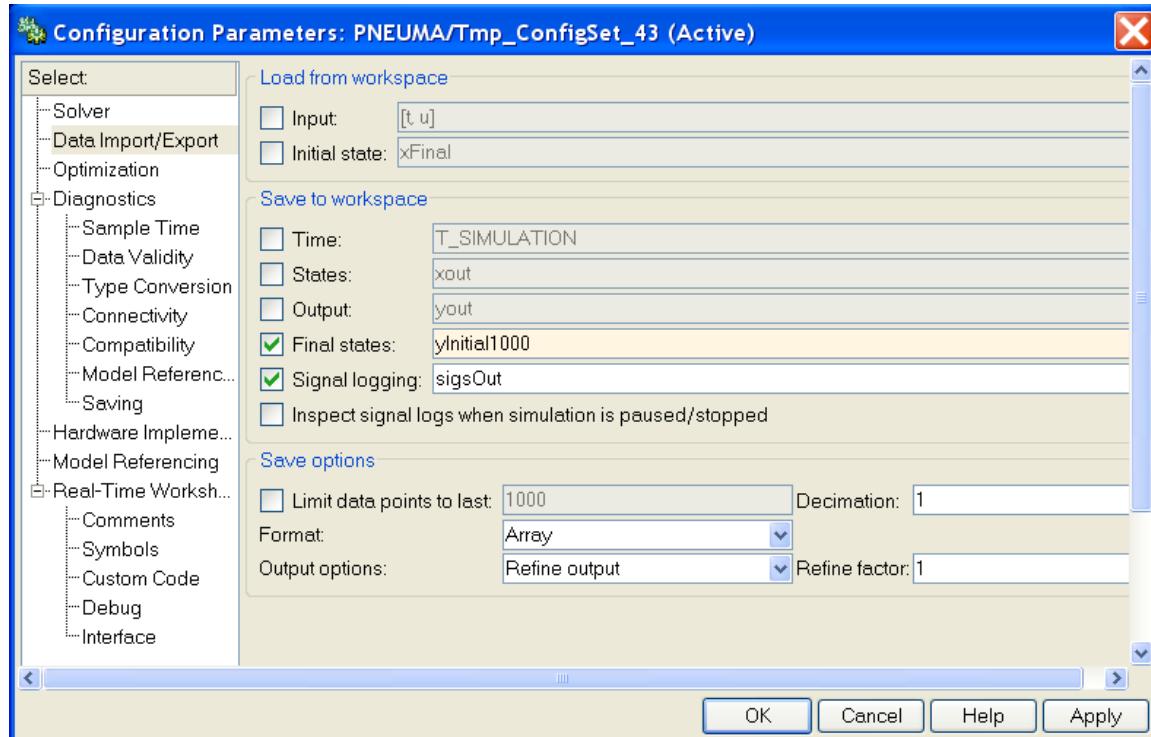
Here is the list of saved data files and the corresponding contents inside the files. Because of the limitations in Matlab® that no data file bigger than 1 GB can be loaded, for the purpose of saving longer time simulation results, the saved data files for each group of data are segmented into 10 small data files naming from ***1.mat to ***10.mat where *** is the data file's name. Each file must be smaller than 1 GB which is large enough for a 10-week simulation (3600*24*70 second run time) with sample period 0.1 sec. However, if the simulation time is longer than 12-weeks (3600*24*84 second run time), then the sampling interval (step duration) must be longer than 0.1 second to ensure each data file is smaller than its limitation 1 GB.

Data File Name	Contents
Autonomic#.mat	Autonomic Control Output Data: ftas_r, ftas_v, ftbs and ftp
BreathingPeriod#.mat	Variable Breathing Period Input/Output Data
CARDIO#.mat	Cardiovascular System Outputs: Heart Period HP, Stroke Volume SV, Cardiac Output CO, TPR and ABP
CARDIORESPIRATORY#.mat	Overall Main Outputs of Cardiorespiratory Interactions: State Drive SI, HR, ABP, Ppl, PaCO2, SaO2, Breathing Frequency BF, Tidal Volume Vt, Total Ventilatory Drive D _{Total}
CircadianProcess#.mat	Circadian Process Data in Sleep Mechanism
deltaFtas#.mat	Insulin Effects on Peripheral Sympathetic Activity
GIMM_FFA_SEC#.mat	Metabolic Model's Inputs and Outputs: G(t), I(t), F(t), E(t), Gin(t), I(t)_in
Nt#.mat	Central Respiratory Neural Drive Nt
PVleft#.mat	Pressure and Volume of Left Atria
Resp_Rhythm#.mat	Respiratory Rhythm Resp_Rhythm
stpres#.mat	Dynamic Drives for Ventilatory Drive: X, Y and Z
TPR#.mat	All the resistances and unstress volumes controlled by alpha-sympathetic activities
varHeartPeriod#.mat	Variable Heart Period Input/Output Data

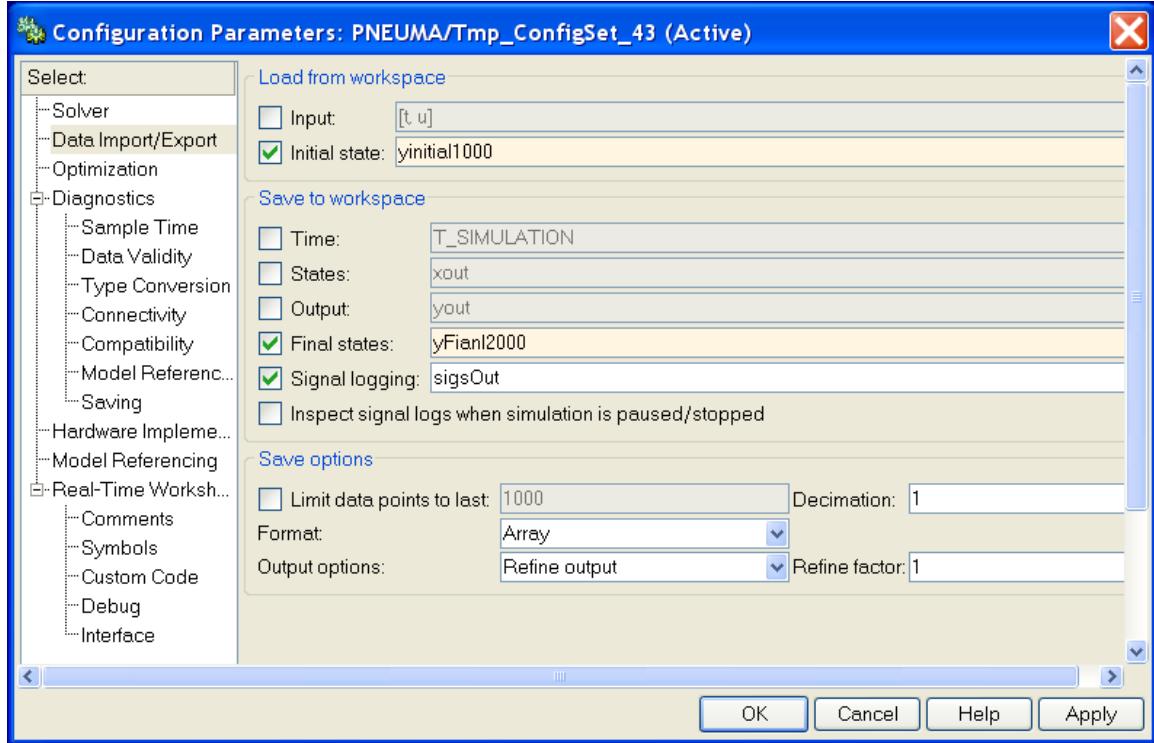
where # represents number 1 to 10 for each data file.

Appendix III: Saved/Load Data for Advanced Users

For the advanced user, a potentially useful option that is available when PNEUMA V.3.0 is run using Matlab® versions higher than R2009a is the ability to load initial states pre-simulation and to save final states post-simulation. This allows for a simulation to be continued starting at the time when the previous simulation run was terminated (assuming the final states have been saved prior to termination). For example, before clicking on “RUN” in the Control Panel for 1000 sec simulation, the advanced user can set up the final state as “yinitial1000” as shown below by opening Configuration in PNEUMA.mdl.



Then, click “Run” to save all the “data” in the workspace when the simulation is stopped at 1000 sec by using “Save Data” in “File” menu. To load these data for the purpose of resuming the simulation run from $t=1000$ sec, modify the configuration as below by checking the box “Initial State” and change its name into “yinitial1000”; to save the final state, modify the configuration as below by checking the box “Final States” and change its name into “yFinal2000” shown as below:



To continuously save/load the states, be sure to provide different names for the initial and final states. Please note that this feature is only available when using PNEUMA V.3.0 in Matlab® versions higher than R2009a.

Appendix IV: Overall Parameter Set and Initial Conditions

Here are the parameters and initial conditions for the complete PNEUMA model. During simulations and before simulations, some of these parameters and conditions can be modified. They are also the parameters/variables in the work space that will be saved into a data file when you select “Save data” under “File”. When you choose “Load data”, those parameters will be loaded into the workspace and some of these parameters/variables will be used as initial conditions in the subsequent simulation. All the saved simulation outputs can be extracted in Matlab® by the user for further plotting or analysis.

Parameter	Definition	Values	Units
Cardiovascular System			
Resistances			
R _{PA}	Pulmonary arterial flow resistance	0.023	mmHg*s/mL
R _{PP}	Pulmonary peripheral flow resistance	0.0894	mmHg*s/mL
R _{PV}	Pulmonary venous flow resistance	0.0056	mmHg*s/mL
R _{SA}	Systemic arterial flow resistance	0.06	mmHg*s/mL
R _{SP}	Splanchnic peripheral flow resistance	3.307	mmHg*s/mL
R _{EP}	Extra-splanchnic peripheral resistance	3.52	mmHg*s/mL
R _{MPN}	Skeletal muscle peripheral flow resistance	4.48	mmHg*s/mL
R _{BPN}	Cerebral peripheral flow resistance	6.57	mmHg*s/mL
R _{HPN}	Coronary peripheral flow resistance	19.71	mmHg*s/mL
R _{SV}	Splanchnic venous flow resistance	0.038	mmHg*s/mL
R _{EV}	Extra-splanchnic venous resistance	0.04	mmHg*s/mL
R _{MV}	Skeletal muscle venous flow resistance	0.05	mmHg*s/mL
R _{BV}	Cerebral venous flow resistance	0.075	mmHg*s/mL
R _{HV}	Coronary venous flow resistance	0.224	mmHg*s/mL
R _{VCA_0}	Nominal vena cava flow resistance	0.025	mmHg*s/mL
R _{LA}	Left atrial flow resistance	0.0025	mmHg*s/mL
R _{RA}	Right atrial flow resistance	0.0025	mmHg*s/mL
Compliances			
C _{PA}	Pulmonary arterial compliances	0.76	mL/mmHg
C _{PP}	Pulmonary peripheral compliances	5.8	mL/mmHg
C _{PV}	Pulmonary venous compliances	25.37	mL/mmHg
C _{SA}	Systemic arterial compliances	0.28	mL/mmHg
C _{SP}	Splanchnic peripheral compliances	2.05	mL/mmHg
C _{EP}	Extra-splanchnic peripheral compliances	0.668	mL/mmHg
C _{MP}	Skeletal muscle peripheral compliances	0.525	mL/mmHg

C_{BP}	Cerebral peripheral compliances	0.358	mL/mmHg
C_{HP}	Coronary peripheral compliances	0.119	mL/mmHg
C_{SV}	Systemic venous compliances	61.11	mL/mmHg
C_{EV}	Extra-splanchnic venous compliances	20	mL/mmHg
C_{MV}	Skeletal muscle venous compliances	15.71	mL/mmHg
C_{BV}	Cerebral venous compliances	10.71	mL/mmHg
C_{HV}	Coronary venous compliances	3.57	mL/mmHg
C_{LA}	Left atrial compliances	19.23	mL/mmHg
C_{RA}	Right atrial compliances	31.25	mL/mmHg
Inertances			
L_{PA}	Pulmonary arterial inertance	0.00018	mmHg*s ² /mL
L_{SA}	Systemic arterial inertance	0.00022	mmHg*s ² /mL
Unstressed Volume			
V_{UPA}	Pulmonary arterial unstressed volume	0	mL
V_{UPP}	Pulmonary peripheral unstressed volume	123	mL
V_{UPV}	Pulmonary venous unstressed volume	120	mL
V_{USA}	Systemic arterial unstressed volume	0	mL
V_{USP}	Splanchnic peripheral unstressed volume	274.4	mL
V_{UEP}	Extra-splanchnic peripheral unstressed volume	134.64	mL
V_{UMP}	Skeletal muscle peripheral unstressed volume	105.8	mL
V_{UBP}	Cerebral peripheral unstressed volume	72.13	mL
V_{UHP}	Coronary peripheral unstressed volume	24	mL
V_{USV}	Splanchnic venous unstressed volume	1121	mL
V_{UEV}	Extra-splanchnic venous unstressed volume	550	mL
V_{UMV}	Skeletal muscle venous unstressed volume	432.14	mL
V_{UBV}	Cerebral venous unstressed volume	294.64	mL
V_{UHV}	Coronary venous unstressed volume	98.21	mL
V_{VC_0}	Vena cava unstressed volume	130	mL
V_{ULA}	Left atrial unstressed volume	25	mL
V_{URA}	Right atrial unstressed volume	25	mL
V_{ULV}	Left ventricular unstressed volume	16.77	mL
V_{URV}	Right ventricular unstressed volume	40.88	mL
Vena Cava			
Kr_{vc}	Gain for vena cava flow resistance	0.001	mmHg*s/mL
V_{vc_max}	Maximum volume of vena cava	350	mL
V_{vc_min}	Minimum volume of vena cava	50	mL
D_1	Parameter for P-V curve of vena cava	0.3855	mmHg
D_2	Parameter for P-V curve of vena cava	-5	mmHg
K_{l_vc}	Parameter for P-V curve of vena cava	0.15	mmHg

K _{2_vc}	Parameter for P-V curve of vena cava	0.4	mmHg
Respiratory System			
Pleural Pressure and Alveolar Pressure			
R _{CW}	Chest wall resistance	1.03	cmH ₂ O*s/L
R _{LT}	Lung transmural resistance	1.69	cmH ₂ O *s/L
R _{AW}	Airway wall resistance	1.016	cmH ₂ O *s/L
E _{CW}	Chest wall elastance	5	cmH ₂ O /L
E _{LT}	Lung transmural elastance	5	cmH ₂ O /L
k _{1,aw}	Constant for upper airway pressure	1.85	cmH ₂ O *s ² / L ²
k _{2,aw}	Constant for upper airway pressure	0.43	cmH ₂ O *s ² / L ²
Gas Exchange and Transport			
Dead Space			
Dead _{(i),co2IC}	Initial condition for i th CO ₂ dead space	39.562	L
Dead _{(i),co2IC}	Initial condition for i th CO ₂ dead space	39.674	L
Dead _{(i),co2IC}	Initial condition for i th CO ₂ dead space	39.813	L
Dead _{(i),co2IC}	Initial condition for i th CO ₂ dead space	40.006	L
Dead _{(i),o2IC}	Initial condition for i th O ₂ dead space	104.36	L
Dead _{(i),o2IC}	Initial condition for i th O ₂ dead space	104.23	L
Dead _{(i),o2IC}	Initial condition for i th O ₂ dead space	104.05	L
Dead _{(i),o2IC}	Initial condition for i th O ₂ dead space	103.8	L
V _{d(i)}	i th dead space volume (i={1..4})	0.03	L
P _{I,CO2}	Inspiratory CO ₂ partial pressure	0	Torr
P _{I,O2}	Inspiratory O ₂ partial pressure	150	Torr
V _{t'}	Respiratory flow	variable	L/sec
V _t	Tidal Volume	variable	L
P _{dO2}	Dead space O ₂ partial pressure	variable	Torr
P _{dCO2}	Dead space CO ₂ partial pressure	variable	Torr
Alveolar Gas Exchange			
V _{co2} , V _{Lco2}	Lungs storage volume for CO ₂	3	L
V _{o2} , V _{Lo2}	Lungs storage volume for O ₂	2.5	L
P _{Aco2IC}	Initial condition for Partial CO ₂ pressure	40.943	Torr
P _{Ao2IC}	Initial condition for Partial O ₂ pressure	102.52	Torr
P _{Ao2IC}	Initial condition for Partial O ₂ pressure	102.52	Torr
P _{ACO2}	Alveolar CO ₂ partial pressure	variable	Torr
P _{ACO2}	Alveolar O ₂ partial pressure	variable	Torr
P _{alv}	Alveolar partial gas pressure	variable	Torr
Q	Blood flow	variable	L/sec
Cardiovascular Transport			
tau _{chemo}	Peripheral chemoreceptors delay time constant	2	s

T_1	Time constant for cardiovascular mixing	1	s
T_2	Time constant for cardiovascular mixing	2	s
T_a	Lung to chemoreceptor circulation delay	variable	s
$LCTV_0$	Lung to chemoreceptor transportation volume constant	0.588	liter
$P_{aO_2\text{first}IC}$	Initial condition for first order P_{ao_2} system	0.3557	Torr
$P_{aO_2\text{second}IC}$	Initial condition for second order P_{ao_2} system	103.14	Torr
$P_{aCO_2\text{first}IC}$	Initial condition for first order P_{aco_2} system	-0.2465	Torr
$P_{aCO_2\text{second}IC}$	Initial condition for second order P_{aco_2} system	40.393	Torr
$P_{aO_2_delay}IC$	Initial condition for O_2 convection	103.12	Torr
$P_{aco_2_delay}IC$	Initial condition for CO_2 convection	40.445	Torr
P_{aCO_2}	CO_2 partial pressure	variable	Torr
P_{aO_2}	O_2 partial pressure	variable	Torr
Cardiovascular Dissociation			
$C1$	Maximum concentration of hemoglobin-bound oxygen	9	mL/mL
$C2$	Maximum carbon dioxide concentration	87	mL/mL
$a1$	Parameter in O_2 dissociation equation	0.3836	dimensionless
$a2$	Parameter in CO_2 dissociation equation	1.819	dimensionless
α_1	Parameter in O_2 dissociation equation	0.02598	dimensionless
α_2	Parameter in CO_2 dissociation equation	0.05591	dimensionless
$K1$	Parameter in O_2 dissociation equation	13	dimensionless
$K2$	Parameter in CO_2 dissociation equation	194.4	dimensionless
β_1	Parameter in O_2 dissociation equation	0.012275	dimensionless
β_2	Parameter in CO_2 dissociation equation	0.03255	dimensionless
$S_{ao_2_delay}IC$	Initial Condition for Oxygen Saturation Delay	98.92	sec
Brain Compartment			
MR_{bco_2}	Metabolic production rate for CO_2 in the brain tissue	0.0517	1/s STPD
S_{co_2}	Dissociation slope for CO_2 in the blood	0.0043	mL/(mL*Torr)
S_{bco_2}	Dissociation slope for CO_2 in the brain tissue	0.36	$mL^*100g^{-1}/Torr$
$P_{bco_2}IC$	Initial condition for partial CO_2 pressure from the brain	48.538	Torr
Body Tissues Compartment			
V_{tco_2}	Body tissue storage volume for CO_2	6	L
V_{to_2}	Body tissue storage volume for O_2	7.7	L
MR_{co_2}	Metabolic production rate for CO_2	0.0033	1/s STPD
MR_{o_2}	Metabolic consumption rate for O_2	0.0038	1/s STPD
$C_{vco_2}IC$	Initial condition for mixed venous CO_2 concentration	0.5247	mL/mL
$C_{vo_2}IC$	Initial condition for mixed venous O_2 concentration	0.1639	mL/mL
Upper Airway Model			

R_{uaw}	Upper airway wall resistance	1000000	cmH ₂ O*s/L
A_{0ua}	Maximum area of opening in upper airway	1	a.u.
K_{ua}	Proportionality coefficient between A_{ua} and Y_{ua} ;	1	L/(s*cmH ₂ O)
P_{crit_awake}	Critical upper airway pressure in wakefulness	-40	cmH ₂ O
S_{ua}	Upper airway sensitivity to collapse	0.01	a.u.
C_{ua}	Upper airway compliance	variable	L/cmH ₂ O
P_{ua}	Upper airway pressure	variable	cmH ₂ O
\dot{V}_{ua}	Upper airway flow	variable	cmH ₂ O
\dot{V}	Total flow in airways	variable	cmH ₂ O
Respiratory Muscle Activity			
FlowIC	Initial air flow	0	L/s
VC	Vital Capacity	5	L
Pt_frcIC1	Initial condition for respiratory muscle reaction	0	spikes/s
Pt_frcIC2	Initial condition for respiratory muscle reaction	0	spikes/s
FlowIC	Initial condition for airflow	0	L/s
VtIC	Initial condition for lung volume	0	L
Central Neural Control			
Carotid Baroreceptors			
Pn	Center pressure for sigmoidal function	92	mmHg
Kcs	Parameter for sigmoidal slope control	11.758	mmHG
Pn_sleep	Parameter for sleep effects	0	mmHg
Kcs_sleep	Parameter for sleep effect	0	mmHG
fcs,min	Lower threshold for sigmoidal function	2.52	spikes/s
fcs,max	Upper saturation for sigmoidal function	47.78	spikes/s
τ_Z	Time constant for baroreflex	6.37	s
τ_P	Time constant for baroreflex	2.076	s
Ventilatory Response			
I_c	Central apneic threshold	45	dimensionless
I_{pCO_2}	Peripheral apneic threshold for CO ₂	38	dimensionless
I_{pO_2}	Peripheral apneic threshold for O ₂	102.4	dimensionless
Gc	Gain for central chemical drive	0.075	dimensionless
Gp	Gain for peripheral chemical drive	0.0063	dimensionless
S_{wake}	Factor of wakefulness to sleep	0.3	dimensionless
Chemoreflex Control of Variable Respiratory Rhythm			
F_b	Basal breathing frequency	12.5	Breath/min
V_b	Basal ventilation	6.7	L/min
T_D	Chemoreflex drive threshold	1539	mL
T_P	Chemoreflex drive threshold	2879	mL

S1 _F	Scaling factor	0.00518	dimensionless
S1 _V	Scaling factor	0.024	dimensionless
S2 _F	Scaling factor	0.0105	dimensionless
S2 _V	Scaling factor	0.0367	dimensionless
Chemoreflex			
fchemo,max	Upper saturation for the sigmoidal function	12.3	spikes/s
fchemo,min	Lower saturation for the sigmoidal function	0.835	spikes/s
fchemo_control	Basal level for the chemoreflex	1.4	dimensionless
Kchemo	Slope control parameter for the sigmoidal function	29.27	mmHg
K _H	Constant value for the static response	3	dimensionless
τ_{chemo}	Time constant for the chemoreflex	2	s
Lung Stretch Receptors Reflex			
Gls	Constant gain	23.29	spikes/sec/liter
τ_{ls}	Time constant	2	sec
Offsets			
X _{sa}	Saturation for the offset of α -sympathetic activity on peripheral resistance	6	Torr
θ_{san}	Nominal level of offset of α -sympathetic activity on peripheral resistance	13.2	spikes/sec
PO2n _{sa}	Central point for the sigmoidal function	30	Torr
kisc _{sa}	Parameter of α -sympathetic activity on peripheral resistance	2	dimensionless
X _{sb}	Saturation for the offset of β -sympathetic activity	21.2	Torr
θ_{sbn}	Nominal level of offset of β -sympathetic activity	3.6	spikes/sec
PO2n _{sb}	Central point for the sigmoidal function	45	Torr
kisc _{sb}	Parameter of β -sympathetic activity	4	dimensionless
X _{sp}	Saturation for the offset of α -sympathetic activity on peripheral resistance	6	dimensionless
θ_{spn}	Nominal level of offset of α -sympathetic activity on peripheral resistance	13.2	spikes/sec
PO2n _{sp}	Central point for the sigmoidal function	30	Torr
kisc _{sp}	Parameter of α -sympathetic activity on unstressed volume of veins	2	dimensionless
τ_{isc}	Time constant for oxygen response	30	s
τ_{cc}	Time constant for carbon dioxide response	20	s
Autonomic Control			
fcs,0	Center point for the sigmoidal function for parasympathetic	25	spikes/s
fpara,0	Lower saturation of the parasympathetic exponential decay function	3.2	spikes/s
fpara, ∞	Upper limit of the parasympathetic exponential decay function	6.3	spikes/s
kp	Slope control parameter for the sigmoidal function	7.06	dimensionless
G_RSA,p	Central RSA gain for parasympathetic response	0.4	dimensionless
Gchemo,p	Chemoreflex gain for parasympathetic response	0.03	dimensionless

Glung,p	Lung stretch receptor reflex gain for parasympathetic response	0.24	dimensionless
$f_{s,0}$	Upper limit of the sympathetic exponential decay function	16.11	spikes/s
$f_{s,\infty}$	Lower saturation of the sympathetic exponential decay function	2.1	spikes/s
Ks	Constant for the exponential function	0.07	s
G_RSA,bs	Central RSA gain for β -sympathetic response	0.4	dimensionless
Gchemo,bs	Chemoreflex gain for β -sympathetic response	2.8	dimensionless
Glung,bs	Lung stretch receptor reflex gain for β -sympathetic	0.24	dimensionless
G_RSA,as	Central RSA gain for α -sympathetic response	0.4	dimensionless
Gchemo,as	Chemoreflex gain for α -sympathetic response	4	dimensionless
Glung,as	Lung stretch receptor reflex gain for α -sympathetic	0.34	dimensionless
β -Sympathetic Response			
ftbsIC	β -sympathetic initial output after time delay	3.8576	spikes/s
ftbs_min	Lower limit for the natural log function	2.66	spikes/s
Gbs	β -sympathetic Gain varied with sleep drive	-0.13	dimensionless
Gbs_sleep	β -sympathetic sleep gain factor	0.2	dimensionless
τ_{bs}	β -sympathetic time constant	2	s
Dbs	Delay for β -sympathetic time constant	2	s
Parasympathetic Response			
ftpIC	Para sympathetic initial output after time delay	4.2748	spikes/s
Gpara	Parasympathetic Gain varied with sleep drive	0.09	dimensionless
Gpara_sleep	Parasympathetic sleep gain factor	0.2	dimensionless
τ_{para}	Parasympathetic time constant	1.5	s
Dbs	Delay for parasympathetic time constant	0.2	s
Neuromuscular Drive			
Inhale	Boolean variable for inhalation	1	dimensionless
Sino-Atrial Node			
HPbasal	Basal value for HP for denervated heart	0.58	s
Maximum End-systolic Elastance			
Glv	Elastance gain for left ventricle	0.475	mmHg /ml/v
D_{lv}	Delay for elastance of left ventricle	2	s
τ_{lv}	Time constant for elastance of left ventricle	8	s
Emax0_lv	Basal level of maximum end-systolic elastance of left ventricle	2.392	mmHg /ml
Grv	Elastance gain for right ventricle	0.282	mmHg /ml/v
D_{rv}	Delay for elastance of right ventricle	2	s
τ_{rv}	Time constant for elastance of right ventricle	8	s
Emax0_rv	Basal level of maximum end-systolic elastance of right ventricle	1.412	mmHg /ml
α -Sympathetic Control of Peripheral Resistance			

fasIC	α -sympathetic initial output after time delay	34.793	spikes/s
fas_min	Lower limit for the natural log function	2.66	spikes/s
Gas_sleep	α -sympathetic Gain varied with sleep	0.3	dimensionless
Gas_sp	α -sympathetic Gain for splanchnic peripheral resistance	0.695	dimensionless
τ_{as_sp}	α -sympathetic time constant	2	s
Das_sp	Delay α -sympathetic time constant	2	s
Gas_ep	α -sympathetic Gain for extra-splanchnic peripheral resistance	1.94	dimensionless
τ_{as_ep}	α -sympathetic time constant	2	s
Das_ep	Delay α -sympathetic time constant	2	s
Gas_mp	α -sympathetic Gain for skeletal muscle peripheral resistance	2.47	dimensionless
τ_{as_mp}	α -sympathetic time constant	2	s
Das_mp	Delay α -sympathetic time constant	2	s
Vusv0	Basal level of unstressed volume of splanchnic venous circulation	1435.4	ml
Gas_usv	α -sympathetic Gain for unstressed volume of splanchnic venous circulation	-265.4	ml/v
τ_{as_usv}	α -sympathetic time constant	20	s
D _{as_usv}	Delay α -sympathetic time constant	5	s
Local Blood Flow Control of Peripheral Resistance			
P _{aCO₂_n}	Nominal arterial CO ₂ partial pressure i	40	Torr
CvO _{2n_b}	Nominal venous O ₂ concentration in cerebral peripheral circulation	0.14	dimensionless
CvO _{2n_m}	Nominal venous O ₂ concentration in skeletal muscle peripheral circulation	0.155	dimensionless
CvO _{2n_h}	Nominal venous O ₂ concentration in coronary peripheral circulation	0.11	dimensionless
Tau_CO ₂	Time constant for peripheral CO ₂ response	20	s
Tau_O ₂	Time constant for peripheral O ₂ response	10	s
A	Parameter for flow regulation equation	20.9	dimensionless
B	Parameter for flow regulation equation	92.8	dimensionless
C	Parameter for flow regulation equation	10570	dimensionless
G _{O_{2_b}}	Gain of local O ₂ response on cerebral vascular bed	10	dimensionless
G _{O_{2_h}}	Gain of local O ₂ response on coronary vascular bed	35	dimensionless
G _{O_{2_m}}	Gain of local O ₂ response on muscular vascular bed	30	dimensionless
Sleep Mechanism			
A	Amplitude of the skewed sine function	20.9	dimensionless
X _H	Bias of the skewed sine function for process CH	0.9	dimensionless
X _L	Bias of the skewed sine function for process CL	0.15	dimensionless
α_{gc}	Constant for sleep decaying	0.2/60	dimensionless
α_{rc}	Rising rate of slow wave activity	0.4/60	dimensionless
α_{fc}	Falling rate of slow wave activity	0.008/60	dimensionless

SWAo	Initial value of sleep wake activity	0.007	dimensionless
Interlink between Metabolic Model and Autonomic Control			
K _{Ce,0}	Gain for basal level of epinephrine in plasma	9	dimension-less
b _{REM}	Gain for REM sleep effect from autonomic control on epinephrine regulations	0.4	dimension-less
a _w	Parameter from autonomic control on epinephrine regulations	0.6	dimension-less
f _{tas,0}	basal firing rate of sympathetic activity	2.1	1/s
K _{as}	Gain of metabolic feedback to change of sympathetic activities	2	dimension-less
f _{tas,I0}	Parameter of metabolic feedback to change of sympathetic activities	1	dimension-less
K _{isc,I}	Parameter of metabolic feedback to change of sympathetic activities	20	dimension-less
τ _I	Time constant of metabolic feedback to change of sympathetic activities	30	min
Plasma Glucose Dynamics			
P ₁	Utilization rate for plasma glucose concentration	0.068	1/min
P ₄	Utilization rate for plasma glucose concentration under the influence of remote insulin	1.3	mL/min /μU
P ₆	Production rate for remote plasma glucose concentration that promotes FFA	0.00006	L/min /μmol
G _b	Basal level of plasma glucose concentration	124.8	mg/dL
Vol _G	Glucose distribution space	117	dL
K _{EG}	Gain from epinephrine to glucose uptake	0.04	dimension-less
Plasma Insulin Dynamics			
n	Utilization rate for plasma insulin concentration	0.142	1/min
P ₅	Factor for insulin inputs	0.000568	1/mL
I _b	Basal level of plasma insulin concentration	16.6	μU/mL
P ₃	Production rate for remote insulin concentration	0.000012	1/min
γ	Insulin sensitivity factor	0.038	μU/mL/min ² per mg/dL
T _{Di}	Variable time delay	5±3	sec
G _h	Threshold of plasma glucose concentration	125	mg/dL
P ₂	Utilization rate for remote insulin concentration	0.037	1/min
P _{F2}	Utilization rate for remote insulin concentration that promotes FFA	0.17	1/min
P _{F3}	Production rate for remote insulin concentration that promotes FFA	0.00001	1/min
X _b	Basal level of remote plasma insulin concentration	0.08125	μU/mL
Y _b	Basal level of remote plasma insulin concentration that promotes FFA production	0.008125	μU/mL
Plasma Free Fatty Acid Dynamics			
P ₇	Utilization rate for plasma FFA concentration	0.03	1/min
P ₈	Utilization rate for remote plasma insulin involved FFA concentration	4.5	mL/min/ μU
F _b	Basal level of plasma FFA concentration	380	μmol/L
Z _b	Basal level of remote plasma FFA concentration	190	μmol/L

k_2	Utilization rate for remote FFA concentration	0.03	1/min
k_1	Production rate for remote FFA concentration	0.02	1/min
Vol_F	FFA distribution space	11.7	L
K_{EF}	Gain from epinephrine to FFA uptake	0.01	dimension-less
Epinephrine Regulation			
E_b	Basal level of epinephrine concentration in plasma	198	pM
τ_E	Time constant for epinephrine regulation	30	min
Δ	Epinephrine regulation factor for metabolic fluxes	1e6	dimension-less
$V_{0,GLC,\text{Heart}}$	Maximum rate coefficient in heart	88	$\mu\text{mol}/\text{min}$
$\lambda_{E,GLC,\text{Heart}}$	Epinephrine regulated flux parameter in heart	3	dimension-less
$\alpha_{E,GLC,\text{Heart}}$	Epinephrine regulated flux parameter in heart	1000	pM
$V_{0,GLY,\text{Heart}}$	Maximum rate coefficient in heart	320	$\mu\text{mol}/\text{min}$
$\lambda_{E,GLY,\text{Heart}}$	Epinephrine regulated flux parameter in heart	0	dimension-less
$\alpha_{E,GLY,\text{Heart}}$	Epinephrine regulated flux parameter in heart	0	pM
$V_{0,FFA,\text{Heart}}$	Maximum rate coefficient in heart	280	$\mu\text{mol}/\text{min}$
$\lambda_{E,FFA,\text{Heart}}$	Epinephrine regulated flux parameter in heart	2	dimension-less
$\alpha_{E,FFA,\text{Heart}}$	Epinephrine regulated flux parameter in heart	447.2	pM
$V_{0,TGL,\text{Heart}}$	Maximum rate coefficient in heart	8	$\mu\text{mol}/\text{min}$
$\lambda_{E,TGL,\text{Heart}}$	Epinephrine regulated flux parameter in heart	0.5	dimension-less
$\alpha_{E,TGL,\text{Heart}}$	Epinephrine regulated flux parameter in heart	1000	pM
$V_{0,GLC,\text{Muscle}}$	Maximum rate coefficient in muscle	398	$\mu\text{mol}/\text{min}$
$\lambda_{E,GLC,\text{Muscle}}$	Epinephrine regulated flux parameter in muscle	18	dimension-less
$\alpha_{E,GLC,\text{Muscle}}$	Epinephrine regulated flux parameter in muscle	1000	pM
$V_{0,GLY,\text{Muscle}}$	Maximum rate coefficient in muscle	1000	$\mu\text{mol}/\text{min}$
$\lambda_{E,GLY,\text{Muscle}}$	Epinephrine regulated flux parameter in muscle	0.3	dimension-less
$\alpha_{E,GLY,\text{Muscle}}$	Epinephrine regulated flux parameter in muscle	10	pM
$V_{0,FFA,\text{Muscle}}$	Maximum rate coefficient in muscle	701	$\mu\text{mol}/\text{min}$
$\lambda_{E,FFA,\text{Muscle}}$	Epinephrine regulated flux parameter in muscle	9	dimension-less
$\alpha_{E,FFA,\text{Muscle}}$	Epinephrine regulated flux parameter in muscle	447.2	pM
$V_{0,PYR,\text{Muscle}}$	Maximum rate coefficient in muscle	80	$\mu\text{mol}/\text{min}$
$\lambda_{E,PYR,\text{Muscle}}$	Epinephrine regulated flux parameter in muscle	2	dimension-less
$\alpha_{E,PYR,\text{Muscle}}$	Epinephrine regulated flux parameter in muscle	1000	pM
$V_{0,TGL,\text{Muscle}}$	Maximum rate coefficient in muscle	260	$\mu\text{mol}/\text{min}$
$\lambda_{E,TGL,\text{Muscle}}$	Epinephrine regulated flux parameter in muscle	2.5	dimension-less
$\alpha_{E,TGL,\text{Muscle}}$	Epinephrine regulated flux parameter in muscle	1000	pM
$V_{0,TGL,\text{GI}}$	Maximum rate coefficient in GI tract	80	$\mu\text{mol}/\text{min}$
$\lambda_{E,TGL,\text{GI}}$	Epinephrine regulated flux parameter in GI tract	2	dimension-less
$\alpha_{E,TGL,\text{GI}}$	Epinephrine regulated flux parameter in GI tract	1000	pM
$V_{0,TGL,\text{adipose}}$	Maximum rate coefficient in adipose	190	$\mu\text{mol}/\text{min}$

$\lambda_{E_TGL_adipose}$	Epinephrine regulated flux parameter in adipose	2	dimension-less
$\alpha_{E_TGL_adipose}$	Epinephrine regulated flux parameter in adipose	1000	pM