Supplemental Information for “Multiscale modeling and data integration in the Virtual Physiological Rat Project”

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**Specific Details on Workflow for Merging of Baroreflex and CV Dynamics Models**

Two software applications are required perform the model identification and merging tasks required in Example 1 of this paper. A third software application was used to view and manually modify the CellML model versions however this will not be necessary for CellML versions that can be imported and compiled directly into JSim.

 JSim v2.05 (download at: <http://www.physiome.org/jsim/download/index.html>)

 SemGen v1.3 (download at: <http://sbp.bhi.washington.edu/projects/semgen>)

 OpenCell v0.8 (download at: <http://www.cellml.org/tools/opencell/>)

All original CellML model files can be found at the CellML model repository ([www.cellml.org](http://www.cellml.org)) and the MML (.mod files), JSim project files (.proj files) and MATLAB files can be downloaded in an archived folder available at the Virtual Physiological Rat Project website ([www.virtualrat.org/VPR1002/](http://www.virtualrat.org/VPR1002/))

*Step 1: CellML model versions to MML.*  The initial versions of the models were uploaded from CellML.org and then imported into JSim to convert each model into an MML model version. (Note: Recent changes in SemGen allow direct import of CellML models and therefore simultaneous conversion to MML and SemSim)

 Baroreflex model CellML Version:

 Original CellML version: download at – [THIS](http://models.cellml.org/exposure/9d046663ba5cac5c8a61ac146183614b/smith_chase_nokes_shaw_wake_2004.cellml/view) – CellML exposure.

 Modifications: No modifications were made to the original CellML version. Import and compilation of the original CellML version were successful.

 Resulting compiled JSim model file: Baroreflex.mod in downloaded archive

 Resulting compiled JSim project file: Baroreflex.proj in downloaded archive

 CV dynamics model CellML Version:

 Original CellML version: download at – [THIS](http://models.cellml.org/exposure/9d046663ba5cac5c8a61ac146183614b/smith_chase_nokes_shaw_wake_2004.cellml/view) – CellML exposure

 Modifications: One modification was made to allow the original CellML version to be imported into JSim and a second modification was required for model compilation. The first modification was made in the OpenCell environment while the second was performed in the JSim environment.

1. To allow successful import the driver function in the original CellML version is converted from:

to:

This change was made because the driver function specified in the original CellML version would only run for 12 periodic cycles and the modified version can run for as many periodic cycles as required through the setting of the time domain.

1. To allow compilation in JSim of the modified and uploaded CellML version one change is required to prevent the model from being over specified. The declaration of Vspt is changed from an externally defined function to a model calculated variable:

extern real V\_spt mL;

is changed to:

real V\_spt(time) mL;

 Resulting modified CellML version: smith\_chase\_nokes\_shaw\_wake\_2004\_modified.cellml in the downloaded archive

 Resulting JSim model file: CVDynamics.mod in downloaded archive

 Resulting JSim project file: CVDynamics.proj in downloaded archive

*Step 2: Import into SemGen and codeword identification.* The JSim model files (.mod files) are imported into SemGen and codewords are unambiguously identified using NCI META Thesaurus, FMA, NCI Thesaurus, OPB, CHEBI, GO and SBO ontologies. It is not necessary to identify all codewords used in the models since detail is only needed to identify the contacting or overlapping regions of the models. Complete identification should be performed in the case where a model is being defined for future unspecified model reuse and merging. The codeword identification of the models can be viewed in SemGen and the files are given below (.owl files):

 Resulting identified Baroreceptor model: Baroreflex.owl in downloaded archive

 Resulting identified CV dynamics model: CVDynamics.owl in downloaded archive

*Step 3: Merging of two models in SemGen.* The identified Baroreceptor and CV Dynamics models are then merged in SemGen. The user determined resolutions are identified in SemGen.

1. The variable A is identified in each model so must be renamed in one of the models. In the Baroreceptor model it represents the cross-sectional area of the aortic lumen and in the CV Dynamics model it is a constant used to calculate the driver function et. The constant is renamed to be A\_Con for the CV Dynamics portion of the merged model in this example.
2. The semantic equivalency between P in the Baroreflex model and P\_ao in the CV Dynamics model as the pressure of blood in the aorta was identified and resolved with the retention of P\_ao.
3. The semantic equivalency between Period in the Baroreflex and period in the CV Dynamics model as the R-R interval was identified and resolved with the retention of Period.

 Resulting Baro/CV Dynamics merged model (SemSim format): BaroCV\_Merged.owl in downloaded archive

*Step 4: Generation of merged model code and modification for simulation.* Once the models are merged in SemGen the SemSim representation can be used to generate MML model code for simulation in JSim. The resulting MML code is given below:

 Resulting Baro/CV Dynamics model (MML format): BaroCV\_Merged.mod in downloaded archive

Five modifications were made to this automatically merged model version to produce the simulation of the Valsalva maneuver in the rat.

1) The Valsalva maneuver was represented in the model with the addition of a 20 mmHg step change in thoracic pressure, P\_th, over a 10 second span.

2) This model was merged from a baroreceptor model parameterized to rat physiology and a CV dynamics model parameterized to human physiology therefore model parameters must be adjusted to one species. In this example we have altered the CV parameters to simulate rat physiologic function. These parameters were evaluated by fitting the CV dynamics model to an independent data set of rat cardiovascular system data. The complete set of altered parameters is given in the Table 1 below.

3) Manual coding was required to add the left ventricle, right ventricle and septum elastances’ dependence on heart rate. This is an improvement on the merged model that represents sympathetic nerve modulation of ventricular contraction.

4) The simple relationship between heart period and heart rate as Period = 60/HR was replaced by a differential equation and the dependence of the function driving heart contraction as a function of heart rate was modified.

5) The resulting new parameter set was determined in terms of units of mmHg instead of kPa so appropriate unit changes were made to the model variables and parameters rather than converting these parameters into units of kPa. This also established a consistent set of units to be used between in the merged model since the Baroreflex model used mmHg. This could have been resolved in the merging process if a consistent set of units and their conversions were made in the original versions of each of the individual models.

All of these changes to the SemGen translation of the merged model are identified with comments in the source code of the following modified JSim project file.

 Resulting Baro/CV Dynamics model with Valsalva: BaroCV\_Merged\_Valsalva.proj in downloaded archive

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **Value** | **Units** | **Reason** |
| *Baroreflex parameters* |
| B3 | 207 | unitless | Rounded to nearest integer |
| HRmax | 483 | beats/min | Rounded to nearest integer |
| HRmin | 226 | beats/min | Rounded to nearest integer |
| HRo | 283 | beats/min | Rounded to nearest integer |
| Tpmax | 3 | arbitrary  | Average SS13BN low salt value from [[1](#_ENREF_1)] |
| Tpmin | 0.5 | arbitrary | Average SS13BN low salt value from [[1](#_ENREF_1)] |
| Zeta | 0.9 | unitless | Linear fit to baroreceptor firing data from [[1](#_ENREF_1)] |
| alpha\_p0 | 76 | Hz | Rounded to nearest integer |
| alpha\_s0 | 59 | Hz | Rounded to nearest integer |
| *CV dynamics parameters* |
| E\_es\_ao | 244.66 | mmHg/mL | Parameterized for rat |
| E\_es\_pa | 37.244 | mmHg/mL | Parameterized for rat |
| E\_es\_pu | 0.49882 | mmHg/mL | Parameterized for rat |
| E\_es\_vs | 0.59847 | mmHg/mL | Parameterized for rat |
| L\_av | 0.0024479 | mmHg\*s2/mL | Parameterized for rat |
| L\_mt | 0.0014814 | mmHg\*s2/mL | Parameterized for rat |
| L\_pv | 0.0065968 | mmHg\*s2/mL | Parameterized for rat |
| L\_tc | 0.0032383 | mmHg\*s2/mL | Parameterized for rat |
| P\_0\_lvf | 0.56285 | mmHg | Parameterized for rat |
| P\_0\_pcd | 3.307 | mmHg | Parameterized for rat |
| P\_0\_rvf | 1.6159 | mmHg | Parameterized for rat |
| P\_0\_spt | 14.609 | mmHg | Parameterized for rat |
| R\_av | 2.57 | mmHg\*s/mL | Parameterized for rat |
| R\_mt | 2.257 | mmHg\*s/mL | Parameterized for rat |
| R\_pul | 22.171 | mmHg\*s/mL | Parameterized for rat |
| R\_pv | 0.7857 | mmHg\*s/mL | Parameterized for rat |
| R\_sys | 155.557 | mmHg\*s/mL | Parameterized for rat |
| R\_tc | 3.386 | mmHg\*s/mL | Parameterized for rat |
| V\_0\_pcd | 1.5093 | mL | Parameterized for rat |
| V\_0\_spt | 0.024019 | mL | Parameterized for rat |
| V\_d\_spt | 0.0083707 | mL | Parameterized for rat |
| lambda\_lvf | 7.6155 | 1/mL | Parameterized for rat |
| lambda\_pcd | 1.5009 | 1/mL | Parameterized for rat |
| lambda\_rvf | 5.1312 | 1/mL | Parameterized for rat |
| lambda\_spt | 53.897 | 1/mL | Parameterized for rat |

Table 1. Parameter changes to merged model to simulate Valsalva maneuver in rat

**References**

1. Bugenhagen, S.M., A.W. Cowley, Jr., and D.A. Beard, *Identifying physiological origins of baroreflex dysfunction in salt-sensitive hypertension in the Dahl SS rat.* Physiological Genomics, 2010. **42**(1): p. 23-41.