PJH 12-May-2019

Proposal for connecting MAP-Core and SIM-Core

To explore possible interaction between the MAP-Core and SIM-Core projects we propose a pilot project for ISAN2019 in which a user of the SPARC web portal could choose a CellML model via the MAP-Core flatmap GUI and set some relevant input(s) for performing a simulation. The model and simulation description (SED-ML) and control script (Python) would be retrieved from the Physiome Model Repository (PMR). This package would be runnable on oSPARC using a MAP-Core provided OpenCOR+Python Docker container. The computational results from the solution of these model equations would be displayed directly on oSPARC and also returned for display on the MAP-Core portal.

We propose creating a flatmap from one of the high level cardiac control diagrams contained in one of Jeff Ardell's papers (see Figure 1) to guide the choice of models. At the top of this control hierarchy are the neurons whose cell bodies are in the central nervous system (CNS) – the brain and spinal cord – which we label **n1** (there could be any number of sequentially linked neurons at this level, but there is at least one from the brain stem medulla to a synapse with a neuron in the T1-T4 segment of the spinal cord). The 2nd level (**n2**) is the link with neurons whose cell bodies are located in a ganglion that sits outside the CNS – for example in the sympathetic chain that includes the stellate ganglion. The 3rd level (**n3**) is for the cell bodies that are located within an organ (in this case the heart), and the 4th level (**n4**) is for the location of neuronal endings on cell receptors such as the β_1 adrenergic receptor that upregulates the production of the second messenger cAMP via the G_s enzyme activation of adenyl cyclase (AC), or the M_2 muscarinic receptor that downregulates cAMP via G_i inhibition of AC (see Figure 1).

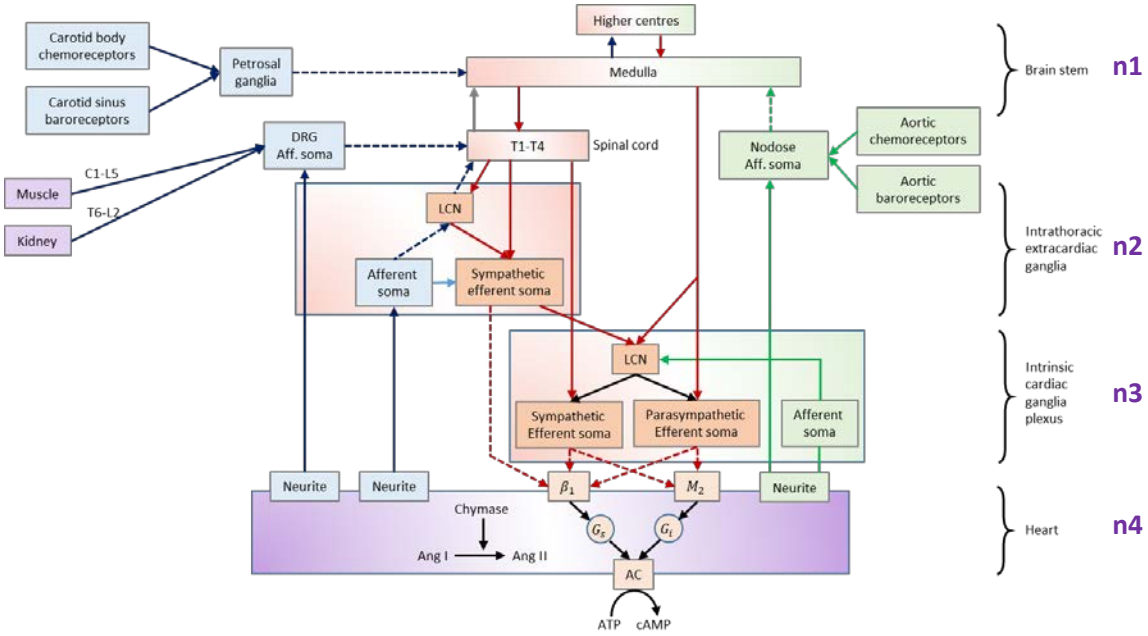

Figure 1. The hierarchy of control identified for the heart by Ardell et al [1] and Kember et al [2]. The n1, n2, n3 & n4 levels shown on the right are defined as follows: Level **n1** corresponds to the central nervous system (the brain stem and spinal cord); level **n2** to the intrathoracic, extracardiac ganglia; level **n3** to the intrinsic cardiac ganglia plexus; and level **n4** to the receptors on cells in the heart.

An example of the location of n1 .. n4 fiducial points on the MAP-Core flatmaps is shown in Figure 2. Note that in this example there are two n1 nodes, one in the medulla and one in the spinal cord. The edges e1, e2, e3, e4 connect the sequence of nodes $n1_1$-$n1_2$-n2-n3-n4.

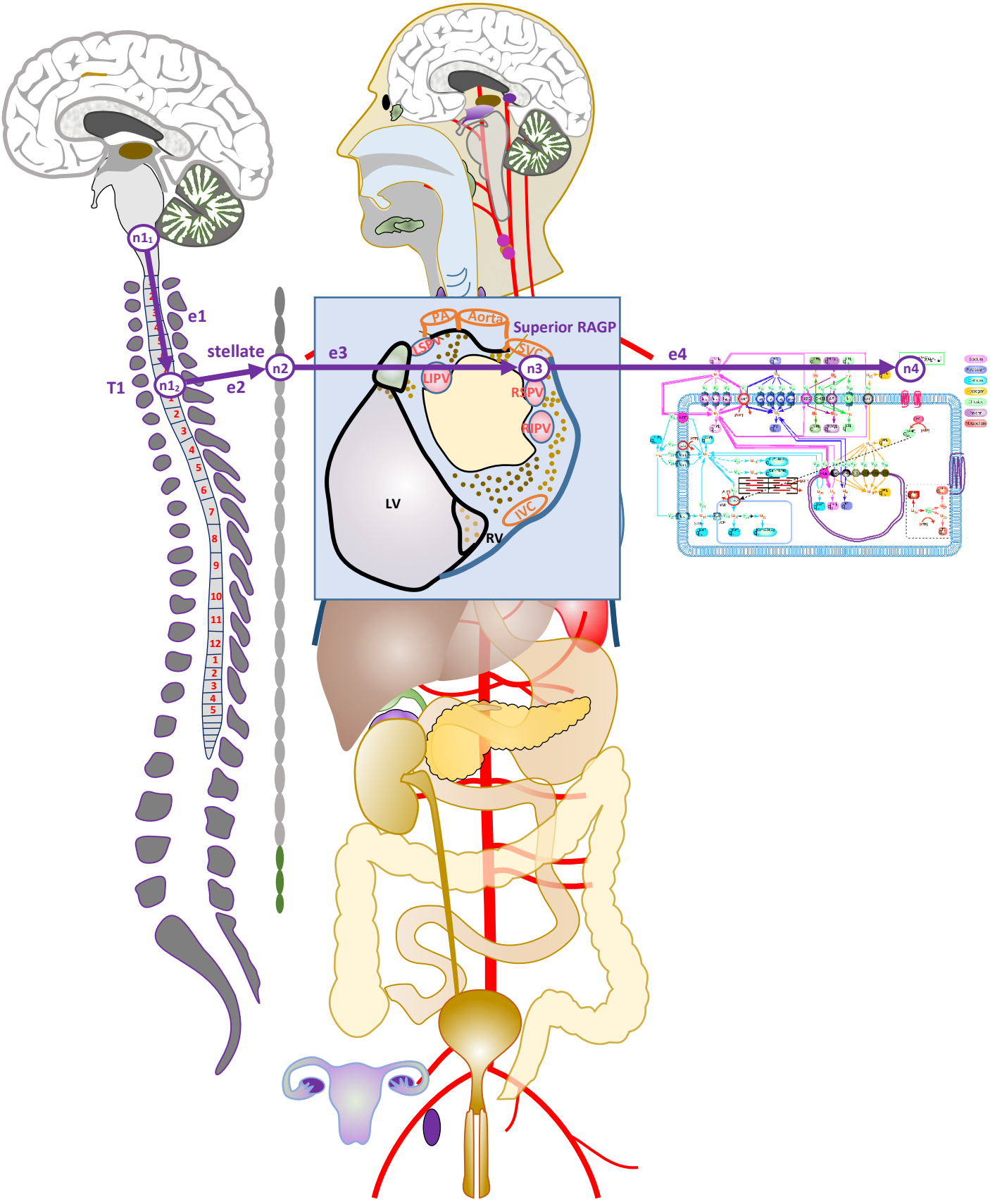

Figure 2. Illustration of a whole body flatmap (centre) and central nervous system map (left) with a neural pathway **n1$_1$-n1$_2$-n2-n3-n4** highlighted to show the neural connections from the brainstem medulla to the β_1-receptor of the sino-atrial node (SAN) cell via the T1 level of the spinal cord, the stellate ganglion, and the right atrial ganglionic plexus (superior RAGP). The

flatmap for the heart is shown in an expanded basal projection to highlight the RAGP. All neural pathways are defined semantically in the knowledge base via fiducial points within a body coordinate system.

We now discuss the models that are either currently available or could be created to define the physiological action at each of the $n1_1$, $n1_2$, n2, n3 and n4 nodes. At this stage it does not matter that these models are overly simple or incomplete, as we are more concerned with the overall strategy for connecting MAP-Core and SIM-Core …. more physiologically realistic models can be added later.

$n1_1$: CNS model

- A model of sympathetic outflow activity in the medulla.

$n1_2$: CNS model

- A very simple neural summation model in the spinal cord.

n2: Synapse models in the peripheral ganglia

- A very simple neural summation model in the stellate ganglia.

n3: Synapse models in the organ ganglionic plexus

- A very simple neural summation model in the right atrial ganglionic plexus (RAGP).

n4: Cellular models containing neuronal receptors

- The Saucerman-McCulloch 2004 model (see Figure 3) which includes a mechanistic description of β-adrenergic regulation of cardiac myocyte mechano-electric coupling [3].

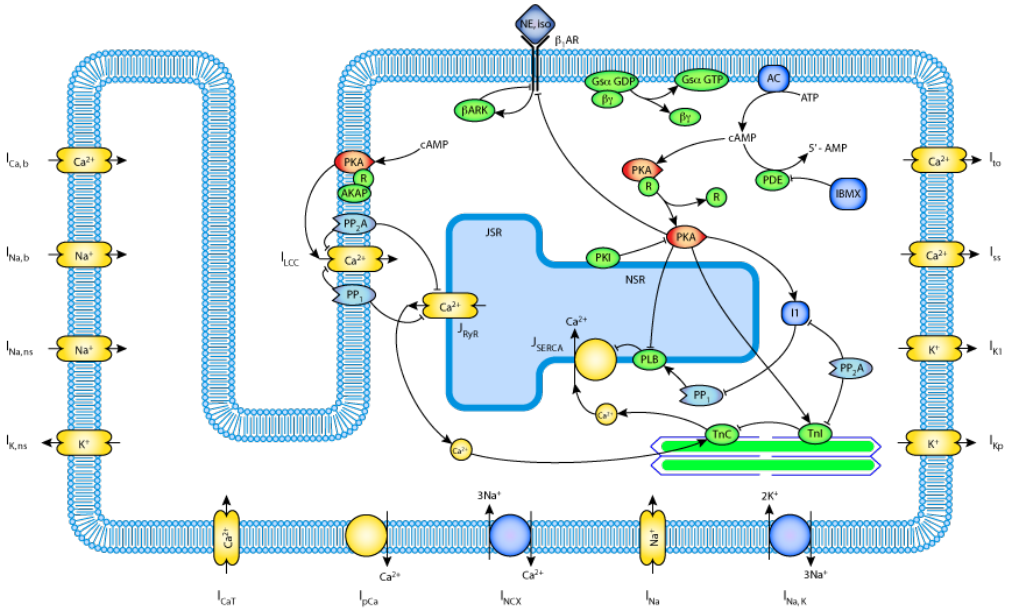

Figure 3. The Saucerman-McCulloch model of β-adrenergic regulation of the cardiac myocyte mechano-electric coupling. The β-receptor corresponds to node n4 of the autonomic system control diagram shown in Figure 1. For the CellML version of this model, see https://models.physiomeproject.org/workspace/563

Our proposed use-case is:

1. The user follows this use-case with the SPARC Data Portal.
2. The user ends up with a viewer showing the control diagram shown in Figure 1 and the relevant flatmaps as shown in Figure 2, including the **$n1_1$-$n1_2$-n2-n3-n4** node sequence.
3. The user is able to select a model from a drop-down list (or similar) that appear when a node is right-clicked, for example. The list of available models is configured automatically based on searching the knowledgebase for relevant models.
4. When the user chooses the **$n1_1$** node, the level of sympathetic drive from the medulla is set via a slider that appears alongside that point.
5. The selected model together with the user-defined level sympathetic drive is sent to the SIM-Core o2S2PARC platform for simulation. Note:

a. The selected model will be defined as a URL to the model and simulation description in PMR (i.e. SED-ML).
b. The level of sympathetic drive will be parameter values that get set in the model prior to simulation.
c. These input parameters are used in a defined workflow on oSPARC which makes use of a MAP-Core supplied OpenCOR+Python Docker container.
d. The workflow on oSPARC results in some relevant simulation results being presented to the user.
e. If the user still has the Data Portal open in the same place then the simulation results could also show up on the portal flatmap viewer, i.e., the action potential is plotted.

6. The computational results are returned and a cardiac myocyte action potential is displayed, for that sympathetic drive input setting, on the MAP-Core portal.
7. The user chooses another sympathetic drive input setting to repeat the procedure.

References

[1] Ardell JL, Andresen MC, Armour JA, Billman GE, Chen PS, Foreman RD, Herring N, O'Leary DS, Sabbah HN, Schultz HD, Sunagawa K and Zucker IH. (2016) Translational neurocardiology: preclinical models and cardioneural integrative aspects. J Physiol 594, 14:3877-3909. DOI: 10.1113/JP271869.

[2] Kember G, Ardell JL, Shivkumar K, Armour JA (2017) Recurrent myocardial infarction: Mechanisms of free-floating adaptation and autonomic derangement in networked cardiac neural control. PLoS ONE 12(7): e0180194. https://doi.org/10.1371/journal.pone.0180194

[3] Saucerman JJ, McCulloch AD. (2004) Mechanistic systems models of cell signaling networks: a case study of myocyte adrenergic regulation. *Progress in Biophysics and Molecular Biology*, Vol 85, 2–3, pp261-278.