Tortuous cardiac intercalated discs modulate ephaptic coupling

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This is the MATLAB source code permitting to replicate the simulations presented in the article entitled "Tortuous cardiac intercalated discs modulate ephaptic coupling" that was accepted for publication in the Journal "Cells" (MDPI, ISSN: 2073-4409).

Download the ZIP file "CodeAndData.zip" and decompress all files into a dedicated folder. The geometrical data of the intercalated disc meshes are located in the subfolder "Meshes".
Details regarding the operation of the scripts and functions are presented briefly below and in detail as comments at the beginning of the scripts/functions as well as throughout the code.
These simulations are optimally run in MATLAB version 2019a on a PC with the Windows 10 operating system, an Intel Core i7 processor and 64 GB of RAM.

Mesh generation

The geometry and the corresponding meshes were generated with COMSOL Multiphysics (version 6.0, COMSOL AB, Stockholm, Sweden). The description of the meshes, including the coordinates of the nodes (vertices) and the element connectivity, were then exported from COMSOL as text files (located in the subfolder "Meshes").
The generation of the COMSOL mesh text files requires a COMSOL license. The COMSOL source files (*.mph files) will be made available upon specific request.

The two-dimensional curved mesh of the intercalated disc can be imported into MATLAB using the script **MainImportMesh.m.** After opening **MainImportMesh.m**, set the variables "Orientation", "Amplitude" and "Number" according to Table 1 and execute the script.

Table 1 : Mesh variables

Variables	Options	Default setting
Orientation	Concentric, Radial, Reference	Concentric
Amplitude of folds ($A = 1/x\ R_{ID}$)	x = 0, 2 , 4, 8, 16	x = 4 ($A = 1/4\ R_{ID}$)
Number of folds (N)	N = 0, 1, 2, 4, 8	4

The script imports the two-dimensional mesh (triangles) into MATLAB variables using the function **importmesh2D.m**. Moreover, the mesh is displayed as a figure and saved as a MATLAB data file (*.mat) file. The execution time takes <1 minute on the system described above. The imported MATLAB meshes, converted into MATLAB data files, will then be used by the main scripts.

Main scripts with their auxiliary functions

Choose and open one of the main scripts (**Main_VoltageClamp.m** or **Main_CurrentClamp.m**), according to the patch clamp protocol that you would like to simulate.

At the beginning of the scripts, set the variables "Orientation", "Amplitude" and "Number" (see Table 1) to choose the intercalated disc folding pattern. Furthermore, to choose the Na^+ channel distribution in the intercalated disc membrane, set the variable "Config" to "uniform" (default for **Main_VoltageClamp.m**) or "cluster" (default for **Main_CurrentClamp.m**). Additionally, set the variables "CleftWidth" (the default width is 30 nm = 0.03*0.0001 cm) and "gapFactor" (fraction of gap junctional coupling relative to normal; use e.g. 0.01 for 1%; default value is 0). Then execute the script. The Results shown in Figures 2, 4 and 5 can be

replicated using **Main_VoltageClamp.m**. To replicate Figure 3, use **Main_VoltageClamp_4points.m**. Moreover, to obtain the Results shown in Figures 6, 7 and 8 execute **Main_CurrentClamp.m**.

Note that the corresponding mesh must first have been loaded and the corresponding MATLAB *.mat data file must have been generated as described above using **MainImportMesh.m**. Otherwise, the program will not find this file.

Depending on the orientation, amplitude and number of folds of the mesh, a simulation (of 3 ms time) takes about 2-7 min on a PC system as described above.

First, the program displays the boundary nodes in a dedicated figure.

Second, during execution, the program displays the extracellular potential (in mV) in the intercalated disc cleft as a color map.

At the end of the simulation, the program produces a figure showing the sodium current in the intercalated disc membranes of the two cells and the minimal extracellular potential in the intercalated disc cleft as a function of time. The script **Main_VoltageClamp_4points.m** executes the same program as **Main_VoltageClamp.m**, but at the end of the simulation, it will also plot the Na^+ current density in both membranes and the extracellular potential at 4 different points in the intercalated disc (with radial coordinates 0, $0.25 \cdot R_{ID}$, $0.5 \cdot R_{ID}$, $0.75 \cdot R_{ID}$ (R_{ID}, being the radius of the intercalated disc).

The script **Main_CurrentClamp.m** additionally shows the intracellular potential of the two cells as a function of time. Furthermore, the program outputs in the MATLAB command prompt the minimal potential in the cleft and, additionally for the script **Main_CurrentClamp.m**, the delay between the two upstrokes of the intracellular potentials.

By repeating simulations using different geometrical folding patterns and parameters, the data and graphics presented in our article can be reconstructed.

The main functions used are briefly described below. For further details, see comments in the MATLAB code.

f_kmf_lintric_inh_3D.m
Computes the stiffness matrix K and the mass matrix M (in sparse format) as well as the load vector F and the area A (non sparse) for a mesh of triangles embedded in 3D space.

f_kmf_lintricontrib_3D.m
Called by **f_kmf_lintric_inh_3D.m**. Computes the finite element contribution to K, M, F and A of a triangle embedded in 3D space.

fCreateUs.m
Creates a sparse matrix of polarized connections. In the jargon of graph theory, this is called the "incidence matrix of a directed graph".

mhjLR1_livshitz.m
This function computes and returns gating parameters for the three gates *m*, *h* and *j* of the sodium current I_{Na} according to Luo and Rudy ("A model of the ventricular cardiac action potential. Depolarization, repolarization, and their interaction." Circ Res 1991, 68:1501-1526) with modifications by Livshitz and Rudy ("Uniqueness and stability of action potential models during rest, pacing, and conduction using problem-solving environment." Biophys J 2009, 97:1265-1276).

The functions **importmesh2D.m**, **f_kmf_lintric_inh_3D.m**, **f_kmf_lintricontrib_3D.m**, **fCreateUs.m** and **mhjLR1_livshitz.m** are identical to those used in a previous project (Ivanovic, Ena, & Kucera, Jan Pavel. (2021). Localization of Na^+ channel clusters in narrowed perinexi of gap junctions enhances cardiac impulse transmission via ephaptic coupling: a model study. Zenodo. https://doi.org/10.5281/zenodo.5226268). The description of these functions is reproduced here verbatim.