In Silico Simulation of Mouse Atrioventricular Conduction Including Sinus Node and Atrial Myocardium

Diego Gazzoni[1], Eugenio Ricci[1], Chiara Bartolucci[1], Stefano Severi[1]
[1] University of Bologna, Cesena, Italy

Abstract

This work aims to investigate mouse atrioventricular node conduction using in silico simulations. First, a 1D cable composed of sinus node, atrium, and atrioventricular node cells was simulated to analyze conduction under healthy and I_f block conditions. No appreciable impairments in atrioventricular conduction were observed, but a surprising increase in atrioventricular node conduction velocity was noted. Next, the focus shifted to the atrioventricular node, with increased resolution achieved by simulating the fast and slow pathways. The fast pathway was hypothesized to consist of half atrial and half atrioventricular node cells, while the slow pathway was made entirely of nodal cells. This model demonstrated the capability of early His activation through the fast pathway, aligning with current knowledge of the mammalian atrioventricular node. Finally, a more complex 2D setup was tested to simulate Koch's triangle in the mouse, including the main atrioventricular node landmarks. In this model, two distinct insulated pathways were not observed, but a slight delay between upper and lower His activation was found, with earlier activation of the upper region.

1. Introduction

The atrioventricular (AV) node is the sole conduction pathway between the atria and ventricles in a healthy heart. In addition to this critical function, it can also pace the heart in cases of sinus node or atrial dysfunction. Despite its vital role, few attempts to simulate the AV node's complete electrophysiology have been made. Inada et. al.'s work on a rabbit AV node model represents a pioneering effort to develop a bio-physically detailed species-specific model for the rabbit [1]. However, no detailed models of the mouse AV node have been reported in the literature to date.

The aim of this work is to propose a novel multi scale mouse AV node model, beginning with a 1D heterogeneous cable composed of sinus node, atrial, and AV node cells, and extending to more complex structures that incorporate dual-pathway AV node electrophysiology. The sensitivity of the proposed models to the funny current (I_f) is also analyzed, with the goal of replicating the findings of Baruscotti et al. [2], who reported progressive AV block and death in mice following HCN4 knockout.

2. Materials and Methods

To build the multiscale models, three species specific models for mouse were used:

- For the *sinus node (SA)*, the Morotti et al. model, based on the Kharche et. al model [3] was used. The source code was taken from Morotti et al. work [4];
- For the *atrial myocadium (AM)*, the Zhang et al. model [5] was used, implemented from scratch;
- The *atrioventricular node (AV)* model is based on our department project [6].

Two cell cables were implemented using discrete models, implemented by connecting cells through ideal resistors to represent the gap junction coupling. The i-th cell is described by a system ODEs, to compute its ion currents I_{ion} and the membrane voltage V_m (eq. (1)).

$$C_m^i \frac{dV_m^i}{dt} = -I_{ion}^i + I_{gap}^i \tag{1}$$

The gap junction current, I_{gap}^i, is computed by considering the M_i neighboring cells, as showed in eq. (2).

$$I_{gap}^i = \sum_{j=1}^{M_i} g_{i,j} \cdot (V_j - V_i) \tag{2}$$

The first setup is a 1D cable made of 100 cells which are 20 SA cells, 50 AM cells and 30 AV cells. The gap junction resistances values are presented in table 2. These values were chosen in order to have the best compromise between conduction velocity comparable to experimental data from Castro et. al.[7] and ability to support propagation along the cable. The second setup represents the AVN as split in a fast pathway (FP) and slow pathway (SP). The FP was hypothesized to be made of half AM and half AV (15 and 15 cells), in order to reproduce the fast conduction along the FP. The SP was hypothesized to be made of only AV cells (30 cells). Both pathways connect into a common sink make of 20 nodal cells (AV). The same number

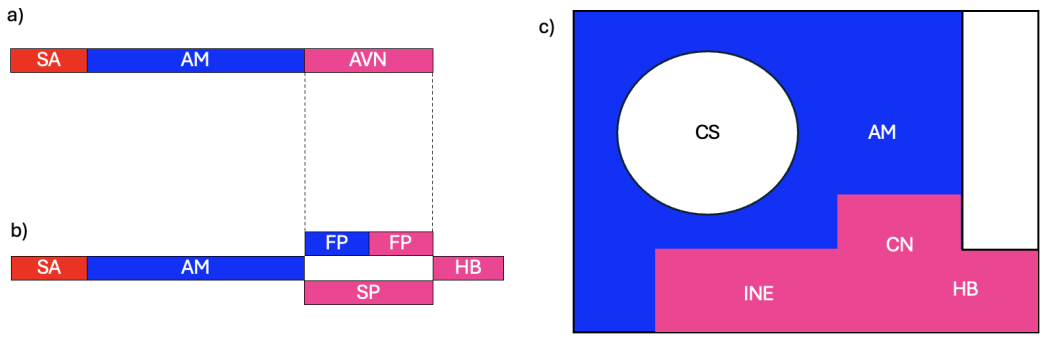

Figure 1. Geometries of different simulated models. (A) represents the 1D cable (B) the dual pathway AVN cable and (C) the 2D tissue. The white regions are non-conductive areas. Here CS = Coronary Sinus Ostium, INE = Inferior Nodal Extension, CN = Compact Node and HB = His Bundle.

	$R_j^{Central}$	$R_j^{Peripheral}$
Sinus Node	130	8.7
Atria	3.5	3.5
Atrioventricular Node	25	25

Table 1. Gap junctions resistances values in MΩ for each district of the cable. 'Central' indicates the leftmost point of the district, while 'peripheral' the rightmost one.

of cells of the previous setup was maintained for the SA node and AM, so the total number of cells is 150.

The third setup is a 2D 25×15 matrix made of AM and AVN cells, organized to reproduce the qualitative shape of the Koch's triangle, including the coronary sinus ostium (CS). The AVN region includes the compact node (CN) and inferior nodal extension (INE). Here all the gap junction values (table 2) are doubled to avoid excessive fastening due to the added dimension.

The models were implemented using Julia programming language [8]. The chosen integrator was *CVODE BDF*. The first two schemes were simulated for 2000ms, while the latter for 1000ms. The data analysis was performed using MATLAB R2024a.

3. Results

3.1. Sinus Node Driving Atrial and AVN Cells

The mouse AVN model conduction capabilities were tested by comparing different levels of I_f block.

The electrical propagation along the cell cable in control conditions is shown in figure 2. The cycle length (CL) is $146\,\mathrm{ms}$, corresponding to approximately 412 bpm. The conduction velocities (CV) are: $3.3\,\mathrm{cm\,s^{-1}}$ in the SA node, $43.4\,\mathrm{cm\,s^{-1}}$ in the AM and $15.4\,\mathrm{cm\,s^{-1}}$ in the AVN.

With a full I_f block (100%), the CL is $183\,\mathrm{ms}$ and

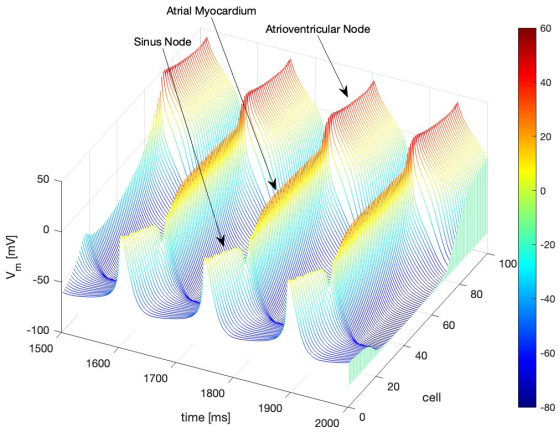

Figure 2. Action potential propagation along the cell cable. From the bottom left to the top right: sinoatrial node (SAN), atrial myocardium (AM) and atrioventricular node (AVN).

so 327 bpm. The CVs are: $4.4\,\mathrm{cm\,s^{-1}}$ in the SA node, $43.4\,\mathrm{cm\,s^{-1}}$ in the AM and $17.4\,\mathrm{cm\,s^{-1}}$ in the AV node.

3.2. Simulating the Dual Pathways

With the dual pathway cable, the first observation is that the fast pathway (FP) drives the downstream load by reaching firstly the His bundle and blocking the pulse in the slow pathway (SP), as shown in figure 3. The cable was tested in control conditions and full I_f block conditions.

In control conditions, the system cycle length is $146\,\mathrm{ms}$, corresponding to 412 bpm. The conduction velocities (CV) are: $3.3\,\mathrm{cm\,s^{-1}}$ in the SA node, $43.3\,\mathrm{cm\,s^{-1}}$ in the AM, $17.6\,\mathrm{cm\,s^{-1}}$ in the SP and $27.5\,\mathrm{cm\,s^{-1}}$ in the FP. The atrial-His (τ_{AH}) time is calculated between the center of the AM and the center of the sink. In this case $\tau_{AH} = 19.2\,\mathrm{ms}$.

With a total I_f block (100%), the system cycle length is 183 ms, so 327 bpm. The conduction velocities (CV) are: $4.4\,\mathrm{cm\,s^{-1}}$ in the SA node, $43.4\,\mathrm{cm\,s^{-1}}$ in the AM, $19.7\,\mathrm{cm\,s^{-1}}$ in the SP and $27.8\,\mathrm{cm\,s^{-1}}$ in the FP. Here $\tau_{AH} = 17.9\,\mathrm{ms}$

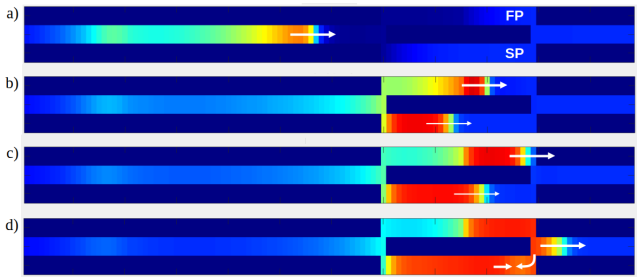

Figure 3. From (a) to (d): action potential propagation along the dual pathway AVN in control conditions. The V_m is proportional to color intensity. The top line is the fast pathway (FP), and the bottom one is the slow pathway (SP). The thick white arrow indicates the main propagation pathways. On (d), it is possible to appreciate a wavefront collision preventing the propagation of the pulse traveling along the SP.

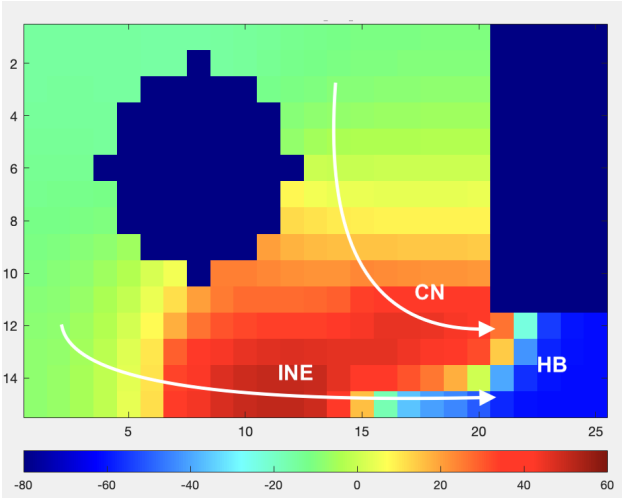

Figure 4. Action potential propagation across the 2D tissue. The arrow coming from the upper-right part, passing from the CN, suggests the fast pathway, while the other one, passing from the INE, suggests the slow pathway. The colorbar indicates the V_m level, while the cell number is indicated on the axes. The dark blue parts are non-conductive areas.

3.3. 2D Simulation of the Koch's Triangle

To initiate the investigation of the complex AVN electrophysiology we simulated a simplified 2D Koch's triangle incorporating a simple AVN that includes the inferior nodal extension (INE), the compact node (CN) and the initial His bundle (HB). The stimulus was artificially delivered at 500bpm on the top-left semi perimeter of the rectangle domain to simulate the arrival from the upper atrial part. The propagation across a portion of tissue is shown in figure 4.

This scheme was tested under both control and 100% I_f block conditions. We computed two atrial-His times, considering the upper and the lower cells of the HB section (cells (21, 12) and (25, 12), figure 4) $\tau^{up}_{AH} = \tau^{up}_{HB} - \tau_{AM}$ and $\tau^{low}_{AH} = \tau^{low}_{HB} - \tau_{AM}$.

In control conditions the two times are $\tau^{up}_{AH} = 5.53\,\mathrm{ms}$ and $\tau^{low}_{AH} = 5.64\,\mathrm{ms}$. The upper-lower difference is $-0.11\,\mathrm{ms}$.

With full I_f block, the two times are $\tau^{up}_{AH} = 5.49\,\mathrm{ms}$ and $\tau^{low}_{AH} = 5.57\,\mathrm{ms}$. The upper-lower difference is $-0.08\,\mathrm{ms}$.

4. Discussion and Conclusions

The 1D simulations demonstrated the capability of our mouse AV model [6] to be integrated and function within a multi scale heterogeneous structure. The adopted gap junction values produced conduction velocity values similar to those reported by Castro et al. [7] for AM and AV, that are $47.0\,\mathrm{cm\,s^{-1}}$ and $16.0\,\mathrm{cm\,s^{-1}}$, respectively.

The insertion of the FP and SP was useful in initiating a more detailed computational study of mouse AV nodal electrophysiology, with the hypothesis that the dual pathway conduction is also present in mice. The primary result is successful replication of the state-of-the-art activation of the His bundle from the FP [9]. Conversely, the 2D simulation of Koch's triangle led to the hypothesis of a more complex conduction pattern across the AVN, suggesting the absence of two insulated pathways.

An analysis was performed on the variation of the maximum conductance of I_f, simulating blocks. Contrary to expectations, the atrioventricular node did not show a reduction in conduction velocity; instead, an increase was observed. This can be attributed to a hyper polarization when I_f is reduced, which might increase the degree of activation of I_{Na}. The conduction block observed by Baruscotti et. al [2] was not reproduced. The significant beating rate reduction of over 50% observed by the cited authors was not achieved. In the one-dimensional scheme, the maximum difference of almost 21% is observed between the control and total block case of I_f, close to what Castro et. al. [7] found in their 1D simulation. This might be due to the chosen SA node model, which could be too resilient to I_f modulation. In the dual pathway scheme, a similar qualitative pattern was recognized: decreasing I_f led to a slight increase in the AVN conduction velocity.

The beating rate variation is practically the same of the mono dimensional case, suggesting that the SA node pacing capability is not affected by the change of load. The unexpected increase in conduction velocity is consistent with $\Delta\tau_{AH} = -1.7\,\mathrm{ms}$ between control and full I_f block cases.

Our 2D simulations did not reveal two insulated propagation pathways. This result might strongly depend on our setup, as a more heterogeneous tissue with conductance modulation and anisotropic gap junctions could potentially lead to different results. Additionally, the early activation of the upper His part might be amplified by increasing the cell number on the vertical axis. Nevertheless, we were able to achieve the atrioventricular conduction with a pseudo-anatomical scheme.

As future development, longer (in time) and larger (in space) simulations could improve the reliability of the data, as our results might not reflect the system's steady state. Secondly, another area for development could involve analyzing how single-cell currents and ion concentrations behave under the proposed conditions, in order to study the role of I_{Na} in the conduction speeding. Additionally, acquiring more data on mouse AVN, including dimensions, geometry and biophysical heterogeneities, could improve the model's agreement with real mouse AVN by simulating more detailed tissue schemes.

To conclude, in our models, I_f did not show an appreciable role in conduction. This could be due to the presence of weaknesses, e.g, the I_f or I_{Na} formulations. However, all the models were able to replicate the mouse AVN electrophysiology in terms of rate and conduction velocities.

Acknowledgments

C.B. and S.S. have received funding from the European Union - NextGenerationEU through the Italian Ministry of University and Research under PNRR - M4C2-I1.3 Project PR 00000019 "HEAL ITALIA" to S.S. CUP J33C22002920006.

References

[1] Inada S, Hancox J, Zhang H, Boyett M. One-dimensional mathematical model of the atrioventricular node including atrio-nodal, nodal, and nodal-his cells. Biophysical Journal October 2009;97(8):2117–2127. ISSN 0006-3495.

[2] Baruscotti M, Bucchi A, Viscomi C, Mandelli G, Consalez G, Gnecchi-Rusconi T, Montano N, Casali KR, Micheloni S, Barbuti A, DiFrancesco D. Deep bradycardia and heart block caused by inducible cardiac-specific knockout of the pacemaker channel gene hcn4. Proceedings of the National Academy of Sciences January 2011; 108(4):1705–1710. ISSN 1091-6490.

[3] Kharche S, Yu J, Lei M, Zhang H. A mathematical model of action potentials of mouse sinoatrial node cells with molecular bases. American Journal of Physiology Heart and Circulatory Physiology September 2011;301(3):H945–H963. ISSN 1522-1539.

[4] Morotti S, Ni H, Peters CH, Rickert C, Asgari-Targhi A, Sato D, Glukhov AV, Proenza C, Grandi E. Intracellular na+ modulates pacemaking activity in murine sinoatrial node myocytes: An in silico analysis. International Journal of Molecular Sciences May 2021;22(11):5645. ISSN 1422-0067.

[5] Zhang H, Zhang S, Wang W, Wang K, Shen W. A mathematical model of the mouse atrial myocyte with inter-atrial electrophysiological heterogeneity. Frontiers in Physiology August 2020;11. ISSN 1664-042X.

[6] Bartolucci C, Mesirca P, Ricci E, Sales-Bellés C, Torre E, Louradour J, Mangoni ME, Severi S. Computational modelling of mouse atrio ventricular node action potential and automaticity. The Journal of Physiology 2024;.

[7] Castro SJ, Colman MA, Kharche S, Wang R, Zhang H. Hcn and scn5a channel mutations: Implications for impaired atrioventricular nodal conduction in a heterogeneous computer model of the whole mouse heart. In Computing in Cardiology 2013. 2013; 41–44.

[8] Bezanson J, Edelman A, Karpinski S, Shah VB. Julia: A fresh approach to numerical computing. SIAM review 2017; 59(1):65–98.

[9] George SA, Faye NR, Murillo-Berlioz A, Lee KB, Trachiotis GD, Efimov IR. At the atrioventricular crossroads: Dual pathway electrophysiology in the atrioventricular node and its underlying heterogeneities. Arrhythmia amp Electrophysiology Review 2017;6(4):179. ISSN 2050-3369.

Address for correspondence:

Stefano Severi
Department of Electrical, Electronic and Information Engineering, University of Bologna
Via dell'Università 50, 47522 Cesena (FC), Italy
stefano.severi@unibo.it