2009

Computer modeling of mouse atrial cell electrophys

Chockalingam, Priya

Chockalingam, P. & Nygren, A. "Computer modeling of mouse atrial cell electrophysiology". 4th Annual Students' Union Undergraduate Research Symposium, November 18-19, 2009, University of Calgary, Calgary, AB.

http://hdl.handle.net/1880/47628

Computer modeling of mouse atrial cell electrophysiology

Priya Chockalingam[1], Anders Nygren[2]

[1]Chemical Engineering with Biomedical Engineering Specialization

[2]Electrical & Computer Engineering and Centre for Bioengineering Research & Education, University of Calgary, Calgary, T2N 1N4

Introduction

Atrial fibrillation (AF) is an abnormal heart rhythm (arrhythmia) that is the most common **cardiac arrhythmia** and affects as many as 10% of people over the age of 75. AF makes heart contraction less effective and increases the risk of stroke by 5 times.

There seems to be currently a lack of fundamental understanding of the underlying mechanisms and causes of AF, making it relatively difficult to design effective therapies. It is important to understand how Action Potential (AP) heterogeneities are affected by disease conditions related to AF and how they can be modulated by antiarrhythmic drugs or "input" from the autonomic nervous system.

In this project, the human heart was analyzed by comparing its functionality with that of a mouse. It has been previously demonstrated that the atria of the mouse heart exhibit heterogeneities in AP properties that are similar to what is known to exist in the heart of larger mammals (presumable including humans)[2].

Goal: To develop a computer model of the **Action Potential**, ion channels and the underlying ionic currents in the human and mouse atrium to compare the effects of disease conditions on AP shape

Methods

Computer simulations were conducted by solving ordinary first order differential equations for action potential occurring in single atrium cells of both the mouse and human heart in a computer program and the output was quantified in terms of **Action Potential Duration (APD)**, **Resting Potential (RP)**, amplitudes of ionic currents, ion concentrations and charges. Using these simulations, the variables in the equations were iterated to observe their effect on atrium rhythm disturbances (AP shape). The mouse atrium model is based on the mouse ventricular model (Bondarenko et al[3]) with certain parameters adjusted to fit the mouse atrium data[1] since the ventricular data is more reliable. Moreover, not many studies have reported about the mouse atria and no published computer model exists for the mouse atrium.

Results

The human atrium has two parts – the Right and the Left Atrium – and separate models were created for each.

The mouse ventricle has 2 parts - the apex and the septum - and separate models were implemented for each. The mouse ventricular model was changed slightly to match the atrial data.

Transformation from Ventricular to Atrial model

Two separate models for the right and the left atrium were created. Major changes made to the mouse ventricle (to obtain the right and left mouse atrium) were the:

- removal of ionic currents like $\mathbf{I_{Kto,s}}$ and $\mathbf{I_{Kr}}$ as there was no evidence of their existence in the atria.
- expression of I_{K1} (time-independent inwardly rectifying K+ current) (to fit the data from Lomax et al[5] using non-linear least square fit), and
- the scaling factors of the RP currents I_{Cab}, I_{Nab}, I_{NaCa}, and I_{NaK}.

In the final atrial model, the ionic currents like $I_{Kto,f}$, I_{Kur}, I_{Kss}, and $I_{Ca,L}$ were adjusted step wise to see their effect on the shape of the AP, APDs and hence their effect on atrium rhythm disturbances.

Table 1: The Resting Potential values for the mouse and the human heart

Cell Type	Resting Potential (mV)
Human atrial myocyte	**-74** (same as theoretical value[2])
Mouse ventricular myocyte	**-82** (same as theoretical value[3])
Mouse right atrial myocyte	**-75**
Mouse left atrial myocyte	**-77**

Action Potentials

Fig 1: Action Potential Graph (AP) for the Mouse Ventricle

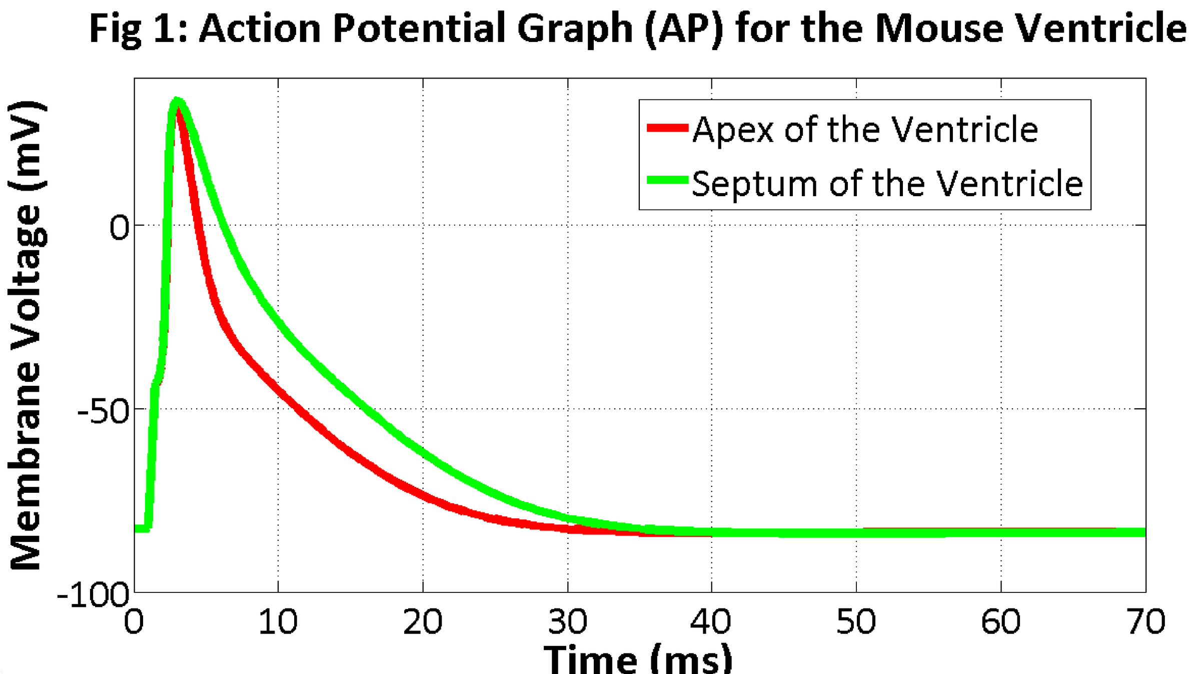


Fig 2: Action Potential Graph (AP) for the Mouse Atrium

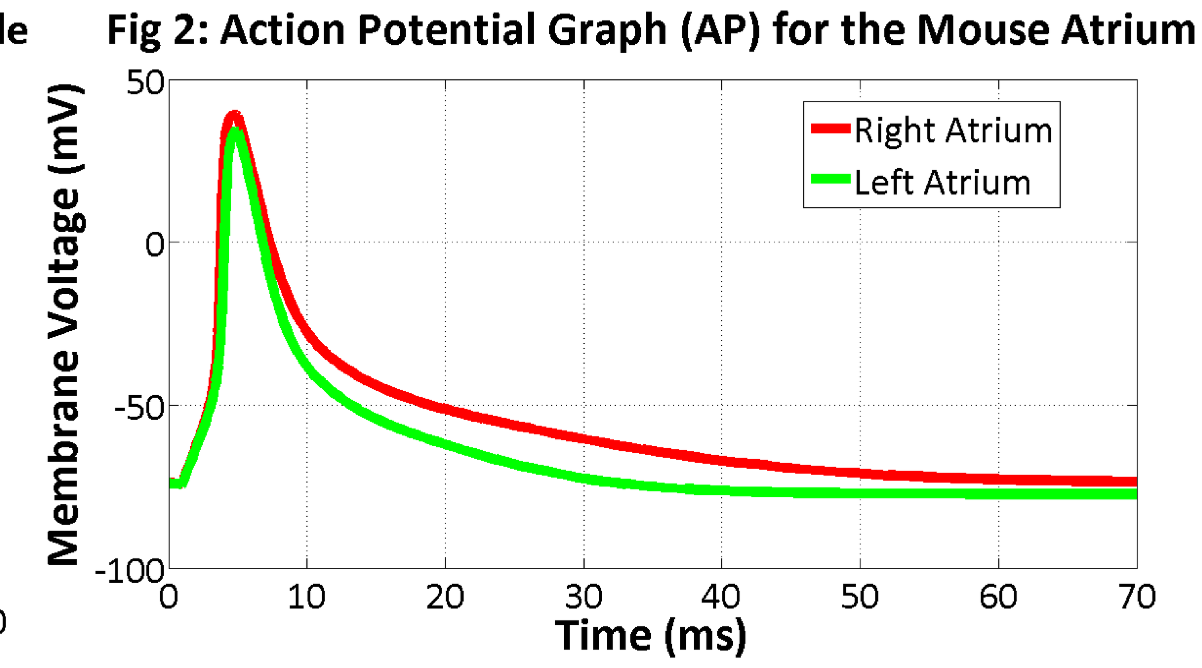
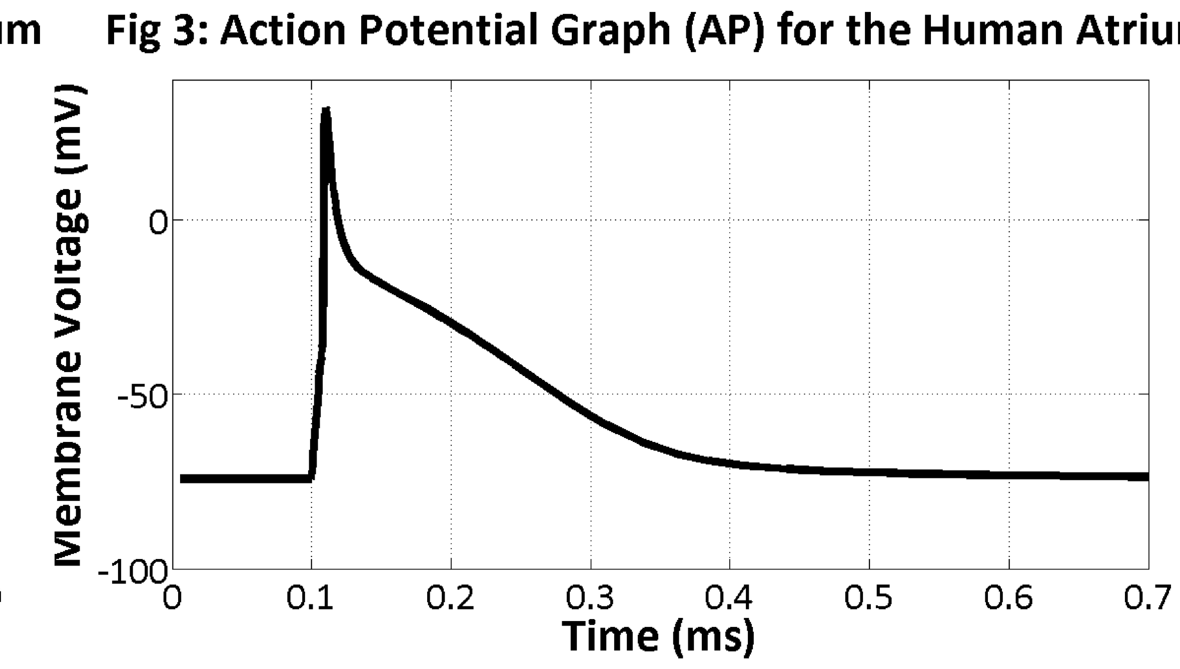
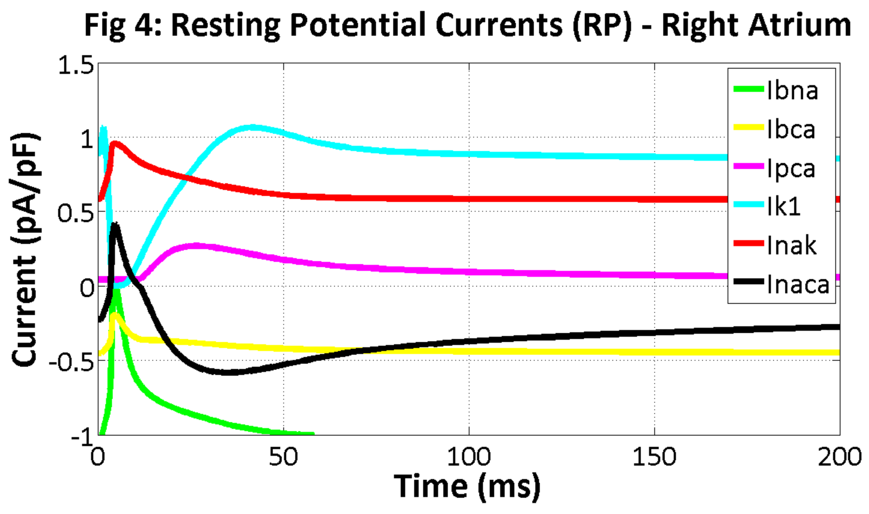


Fig 3: Action Potential Graph (AP) for the Human Atrium



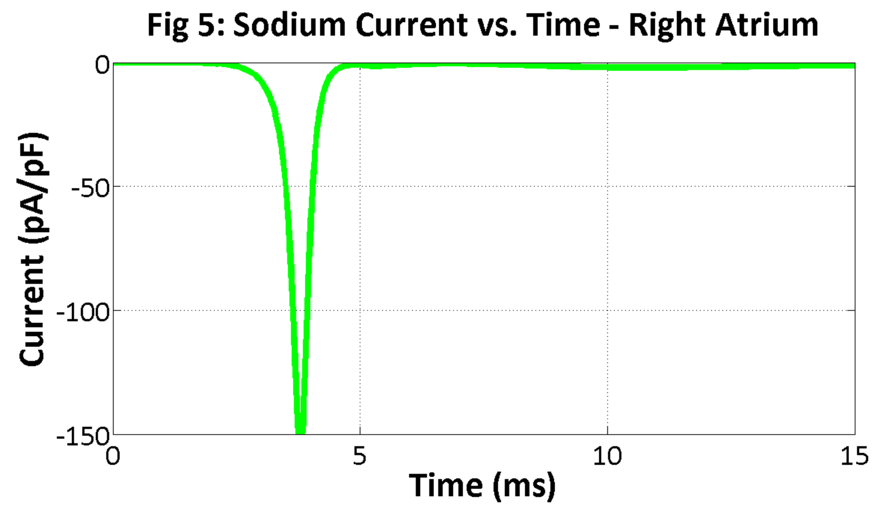
Mouse Atrial Ionic Currents

Fig 4: Resting Potential Currents (RP) - Right Atrium



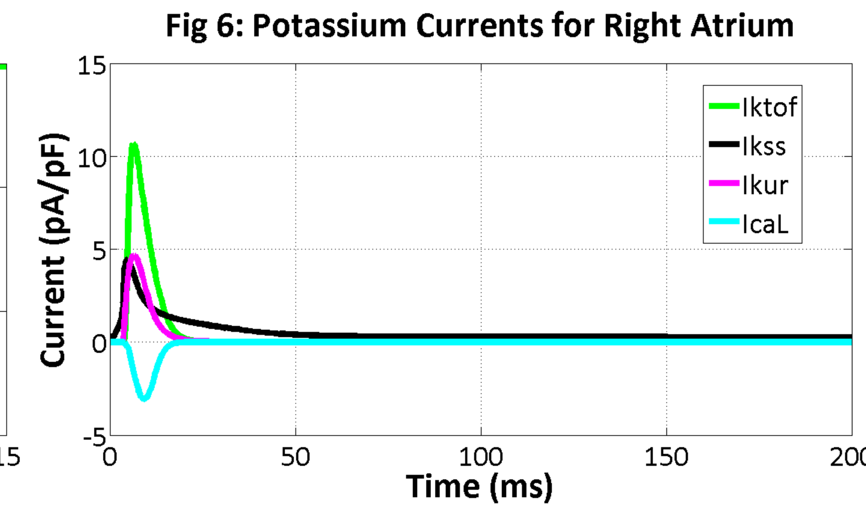
- The RP of the Right Atrium is -75 mV which is closer to the theoretical value of -74 mV.
- Hence, the ionic currents of the Right Atrium are displayed

Fig 5: Sodium Current vs. Time - Right Atrium



- The RP currents maintain the RP of the myocyte
- The Sodium Current causes depolarization of the adjacent myocytes

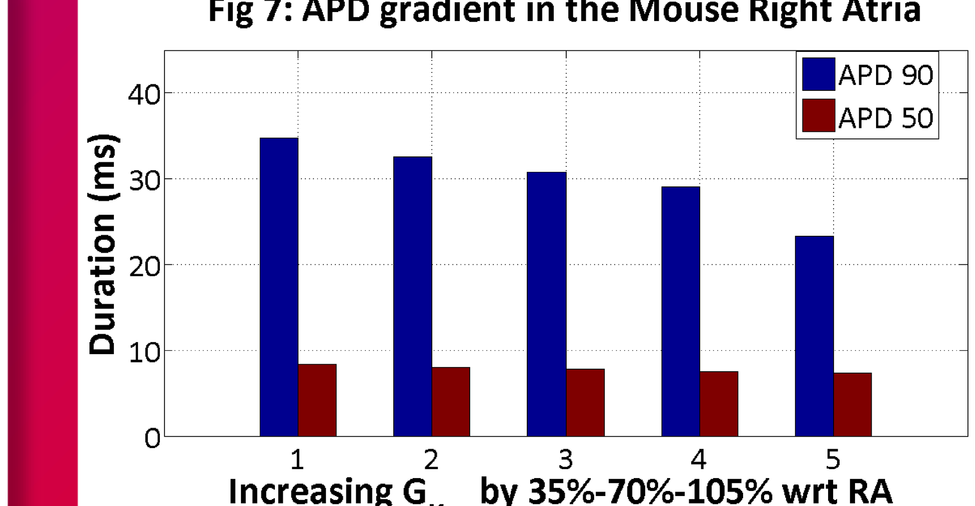
Fig 6: Potassium Currents for Right Atrium



- The Potassium Currents influence the APD of the myocytes (width of AP)

Action Potential Duration

Fig 7: APD gradient in the Mouse Right Atria



- The right most represents the Right atrium APD and the left most represents the Left atrium APD. The middle portion represents the intermediate region

Conclusion

- The RP values for the mouse and human heart are summarized in Table 1.
- The computer model results show that increasing $\mathbf{I_{Kur}}$ decreases the APD and blocking it completely increases the APD by 7ms.
- Similarly, decreasing $\mathbf{I_{Ca,L}}$ decreases the APD.
- The same analysis was applied to the ionic currents like $\mathbf{I_{Kto,f}}$ and $\mathbf{I_{Kss}}$.

Further Study

The computer models of the Action Potential, ion channels and the underlying ionic currents in the human and mouse atrium developed can be used as a tool to investigate arrhythmias in the mouse heart and contribute new insights into the underlying mechanisms like action potentials, ion channels and ionic currents in the mouse atria. This can eventually contribute to find the real cause of the disease, and develop enhanced treatment therapies for people suffering from this disease all over the world.

References

[1]"Computer model of the Action Potential and Underlying Ionic Currents in the Mouse Atrium". Laila Jahan, U of C 2008.

[2]A.Nygren, A.E. Lomax, W.R. Giles. Heterogeneity of action potential durations in isolated mouse left and right atria recorded using voltage-sensitive dye mapping. *Am J Physiology* 2004; 287:H2634-43.

[3]V.E.Bondarenko, G.P.Szigeti, G.C.Bett, S.J.Kim, and R.L.Rasmusson. Computer model of action potential of mouse ventricular myocytes. *Am J Physiol Heart Circ Physiol* 2004 September; 287(3):H1378-H1403.

[4]A.Nygren, C.Fiset, L.Firek, J.W.Clark, D.S.Lindblad, R.B. Clark, W.R. Giles. Mathematical Model of an Adult Human Atrial Cell. The Role of K+ Currents in Repolarization. *Circulation Research* 1998; 82:63-81.

[5]A.E.Lomax, C.S.Kondo, and W.R.Giles. Comparison of time- and voltage-dependent K+ currents in myocytes from left and right atria of adult mice. *Am J Physiol Heart Circ Physiol* 2003 November; 285(5):H1837-H1848.

Acknowledgments

The authors would like to acknowledge the support of PURE and the members of School of CARP. Thanks to Ms.Laila Jahan for her MSc Thesis on which the parameter adjustments for the mouse atrial model were based.

If you have any questions, please feel free to contact the author at pachocka@ucalgary.ca.