Relationship between the occurrence of EADs and non-excitable gap size

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Abstract

Early afterdepolarizations (EADs) are the abnormal oscillations during the plateaus phase of the cardiac action potential (The change in membrane voltage across the sell membrane of heart cells), which have the indisputable relationship with cardiac arrhythmias. And EADs in heart tissue will trigger the action potential in neighboring cells. In this project, we are aiming to find the desire condition where the EAD will happens and then digging into that point and find the relationship between the formation of EADs and other factors, including essential elements that affect the propagate of action potential wave, and the geometry shape of excitable cells.

Introduction

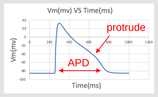
The heart is one of the most complex organs in the body. When the heart is beating, the electrical action potential waves propagate periodically in tissue. Under normal conditions, the wave propagates smoothly without interruptions. However, under pathological conditions, the propagation can be disturbed and may form spiral waves (ventricular tachycardia) or spatiotemporal chaos (ventricular fibrillation). In this study, we investigated how the propagation of action potential wave and the tissue geometry will affect the formation of EADs. The graphs below shows the propagation of action potential wave is tissues. The horizontal and vertical tunnel represent the excitable cells and the width of them are defined by the number of excitable cells, which could be called incoming width and gap width. The difference of the width could be described as “source-sink mismatch,” which can promote the formation of EADs. If the source-sink mismatch is too small, the action potential wave propagates normally with a small delay. If the source-sink mismatch is too large, the action potential wave cannot propagate. As a result, we aiming to find the desire incoming width and gap size where the EAD will happens and then digging into that point and find the relationship between the formation of EADs and other factors, including essential elements that affect the propagate of action potential wave, and the geometry shape of excitable cells.

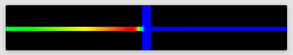
* The warmer color is, the higher the Membrane Voltage at that moment

Action Potential wave propagated

Incoming tissue width: **10** excitable cells
Gap tissue width: **8** excitable cells
(Large to small)

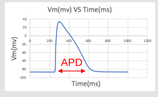
Membrane Voltage(mv) VS Time(ms)





Action Potential wave cannot propagate

Incoming tissue width: **10** excitable cells
Gap tissue width: **20** excitable cells
(small to large)

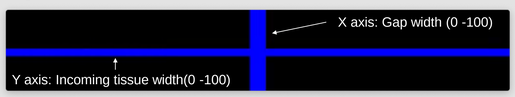


From the Membrane Voltage vs Time graph, both these two propagations do not trigger the EAD(the source-sink mismatch is not desire), we can only see one bump in the graph. However, in the first simulation when the action potential wave propagated successfully, the Action Potential Duration(APD) labeled in graph is larger than it in the second simulation, and there is a small protrude which will become an EAD in the future when other requirement achieved.

Materials and Methodology

Our research was based on the C++ program , which can simulate the propagation of action potential wave among tissues with changeable sizes by calculating the Membrane Voltage of each time period using Runge-Kutta Method(which will male the simulation more precisely). The program can generate both the data(including the Membrane Voltage of each time period) and the video of the whole propagating process based on the given parameters in a considerably short amount of time by using OpenMP(multiprocessing programming API). Important elements required for simulation can all be modified, including the simulate time, cell excitability, sample size etc. Besides, the geometry shape of the tissue could be modified and generate corresponding videos and datasets.

In order to find the relationship between source-sink mismatch and the propagation of action potential wave. We decide to vary the incoming tissue shape and the shape of the gap literately from size 1 (excitable cells)to 100 (excitable cells) and observe the behavior of action potential wave. The table is attached below. The values on horizontal axle are the widths of incoming tissue and the vertical axle represent the gap width. Then, we changed some important input values of generating action potential waves and the tissue shape in order to find patterns.



The content in the grid could be 0 or 1:
0: The Action Potential wave cannot propagate.
1 : The Action Potential wave propagate propagate successfully.

Horizontal axis:
Incoming tissue size (number of excitable cells)

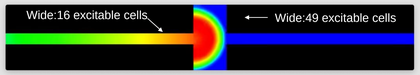
Vertical axis:
Gap tissue size(number of excitable cells)

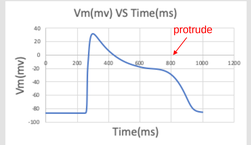
o/i	1	2	3	4	5	6	7	8	9	10	15	20	25	30	50	100
1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1
4	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1
5	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1
6	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1
7	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
8	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
9	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
10	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
15	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
20	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
30	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1
50	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1
100	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1

Incoming tissue width: 16 excitable cells

Results

From the table and the simulation, we found that the point where the incoming tissue size is 16 (excitable cells) will be the edge point distinct whether the action potential wave will propagate successfully regardless how wide the gap be. The reason for that could be that when the incoming cell width is 16 cells, the action potential wave will have enough energy to excite its neighbor cells and reach the edge of our workspace(The vertical width is 100 excitable cells). Once it reach the edges, the excitation of other cells in the gap could be much easier. In the end, the action potential wave will cross the gap and the propagation will success. At this point, the screen shot of propagation and the Vm vs Time plot shown below:



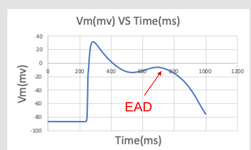


From the graph on the left, the protrude is much obvious than before but there is still not a bump which represent the emergence of EAD. At this time, we changed the diffusion coefficient constant of voltage(D), which due to the current from neighboring cells through gap junction, higher and make the propagate of action potential from cells to cells easier and expect to observe the formation of EADs.

$$\frac{\partial V(x,t)}{\partial t} = -s(x) \cdot \frac{I_{ion}(x,t)}{Cm} + \nabla \cdot D \nabla V(x,t)$$

Membrane potential — diffusion coefficient constant

Finally, by adjusting the diffusion coefficient constant (D) from default 0.0005 (cm^2/s) to 0.00055 (cm^2/s), we observe the emergence of EAD(D value is 10% larger than the default setting). The Vm vs Time plot is shown below.

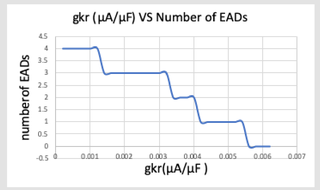


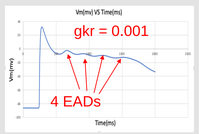
From the graph on the left, a bump Is clearly shown, and this is where the Early Afterdepolarization happens, the abnormal oscillation of membrane voltage during the plateau phase of the cardiac action potential wave.

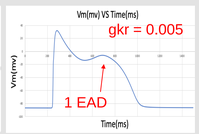
After figuring out the fundamental requirements for the formation of the first EAD, we now want to know how the value of rectifier channels which influence the formation and propagate of cardiac action potential will influence the formation of EADs. At this phase, we choose the slow delayed rectifier K+ channels (represented by Iks) and the rapid delayed rectifier K+ channel(represented by Iks) as our research object. In order to modify the current Iks and Ikr, we can simply modify their conductance, gkr and gks.

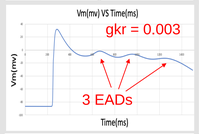
➢ Relationship Between gkr (Ikr conductance) and EAD

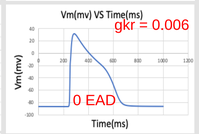
By adjusting the value of gkr (conductance of Ikr) in the range 0.0002 μA/μF to 0.0062 μA/μF (originally 0.005 μA/μF), and observe the occurrence of EADs from the Vm-Time graph, we found that when gkr's value becomes larger, The number of EADs decrease, however, numbers of EADs will increase when the gkr's value goes down, and EAD will not occur when the value is larger than 0.0056 μA/μF.

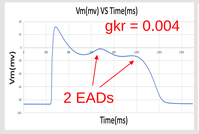


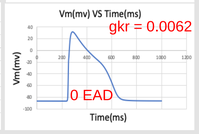








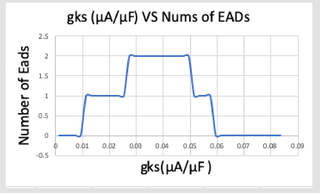


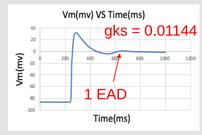


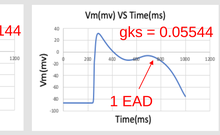
The left part is V vs T graph of different gkr (conductance of Ikr) values. The peeks pointed by the arrow are the EADs. As we decrease the conductance of kr current, The value of kr current will goes down. And this decreasing current promote the formation of EADs. from the changing rate of the wave around the peek, you can see that the change on membrane voltage is more visible as the value of gkr goes down. Meanwhile, the APD also become larger

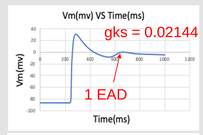
➢ Relationship Between gks (Iks conductance) and EAD

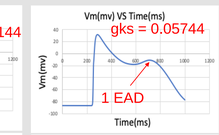
By adjusting the value of gks (conductance of Iks) in the range 0.00144 μA/μF to 0.008344 μA/μF (originally 0.005 μA/μF), and observe the occurrence of EADs from the Vm-Time graph, we found that when gks's value becomes larger or smaller than the value 0.003844, the number of EADs decreases.

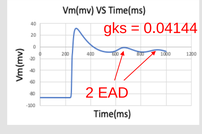


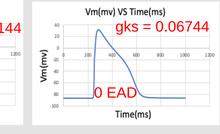








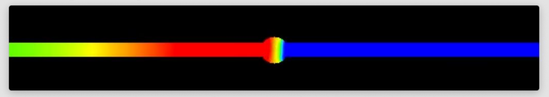




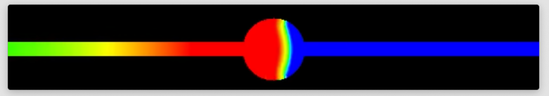
The left part is V vs T graph of different gks (conductance of Iks) values. The peeks pointed by the arrow are the EADs. As we decrease the conductance of ks current, The value of kr current will goes down. And this decreasing current promote the formation of EADs. This will also happen when we increasing the conductance of ks current. When the gks value is the range 0.02944 μA/μF - 0.05044 μA/μF , the Number of EAD reach its maximum times, 3 times.

➢ Relationship Between Geometry shape, Propagations and EADs.

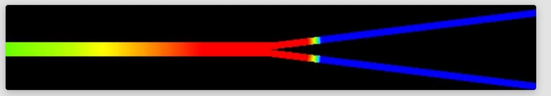
From the sample simulation where we changed the diffusion coefficient constant of voltage(D) to 0.00055 (cm^2/s), we want to figure out the influence of tissue shape on the formation of EADs. As a result, we only changed the shape of excitable cells and keep other factors unchanged. We simulated the bidirected shape, ball shape, and the spindle shape.



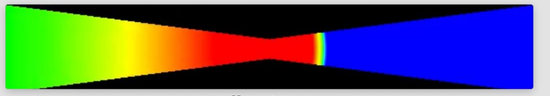
Square Rad = 15



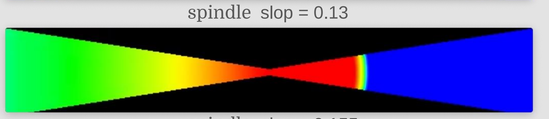
Square Rad = 35



Bidirected



spindle slop = 0.13



spindle slop = 0.155

Rad = 35

Bidirected

spindle, slop = 0.13

However, based on the simulation we make. There is no EAD occurs in any of those model we simulated. Although the membrane voltage vs time graph of bidirected tissue size have a considerably longer APD, the EAD did not happened. In the future, we may simulate more geometries shapes and try to change some elements that will influence the propagate of cardiac action potential in order to see the EAD happens.

Conclusion and Next Step

I our research, we have simulated and get the request of success propagation of action potential waves. Besides, we also found the relationship between the changing of gkr's value and gks's value with the occurrences. Moreover, by simulate different excitable cell shapes, we also reveal the relationship of EADs with some given tissue shapes. The further study could focus on the more complicated tissue shapes or even the irregular bound shape, which is more simulate with the real tissue shape in human body. We wish we can finally find an equation of the occurrence of EADs with given variables like gap size, gkr's value, gks's value, etc.

Acknowledgements

Thanks for Professor Daisuke Sato for academic help, guiding and suggestion, members in Sato's Lab for suggestions and _____ for the starting code.