David Young
SID #: 420451
1/28/2013

CLAB 1: Cardiac Action Potential

Problem 1.1:

```
load 1000x100
v = States(:,1);                    % voltage data saved in column 1
cai = States(:,8);                  % intracellular calcium saved in column 8

t_a=31282;                          %index of starting time for the last beat
t_b=31592;                          %index of ending time for the last beat


t2plot=t(t_a:t_b,1)'-t(t_a);        %row vector of times from the last beat
v2plot=v(t_a:t_b,1)';               %row vector of voltages from the last beat
cai2plot=cai(t_a:t_b,1)';           %row vector of cai from the last beat

%Problem 1.1:  plot voltage and intracellular calcium vs time...
subplot(2,1,1);
plot(t2plot,v2plot);
grid on;  title('Voltage vs. Time','Fontsize',12);  xlabel('time (ms)');
ylabel('Voltage (mV)');

subplot(2,1,2);
plot(t2plot,cai2plot);
grid on;  title('Intracellular Ca2+ Concentration vs. Time','Fontsize',12);
xlabel('time (ms)');ylabel('Intracellular Ca2+ Concentration(mM)');
```

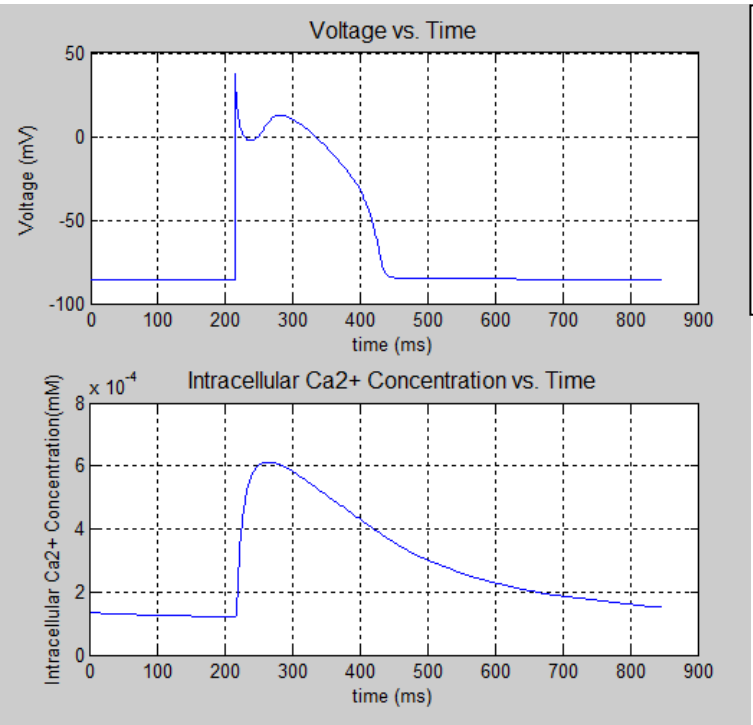


Figure 1:
Entire time course of action potential (above) and simultaneous time course of Intracellular Ca^{2+} concentration (below) obtained from the last beat of a 100 beat model simulation of cardiac action potential.

Problem 1.2:

```
%calculate the values specified in lab manual problem 1.2, then save them
%for later use in problem 3 as elements in a control vector
V_rest=v2plot(1);
V_max=max(v2plot);
Y=diff(v2plot)./diff(t2plot);     %first derivative of voltage
dvdt_max=max(Y);
CAI_max=max(cai2plot);

prob_3_control=[dvdt_max,CAI_max,V_max,V_rest];
```

1.2 Results

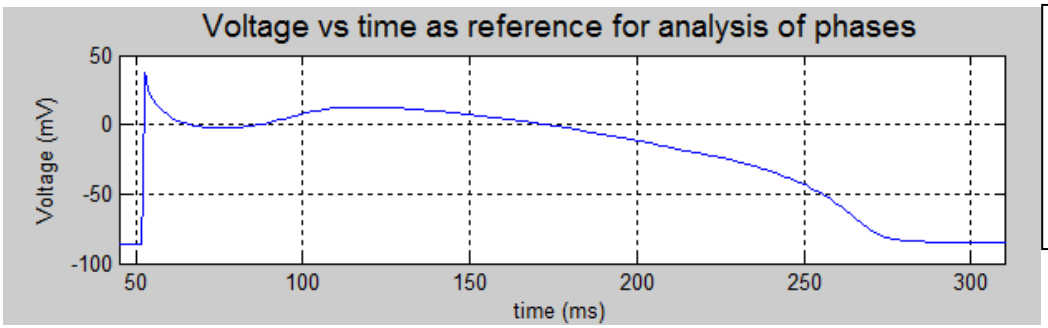
Vrest	37.9287 mV
Vmax	37.9287 mV
dV/dT max	272.6017 mV/ms
$[Ca^{2+}]_i$max	0.0006 uA/mF

Table 1:
Shows the results of different parameters from the previous simulation

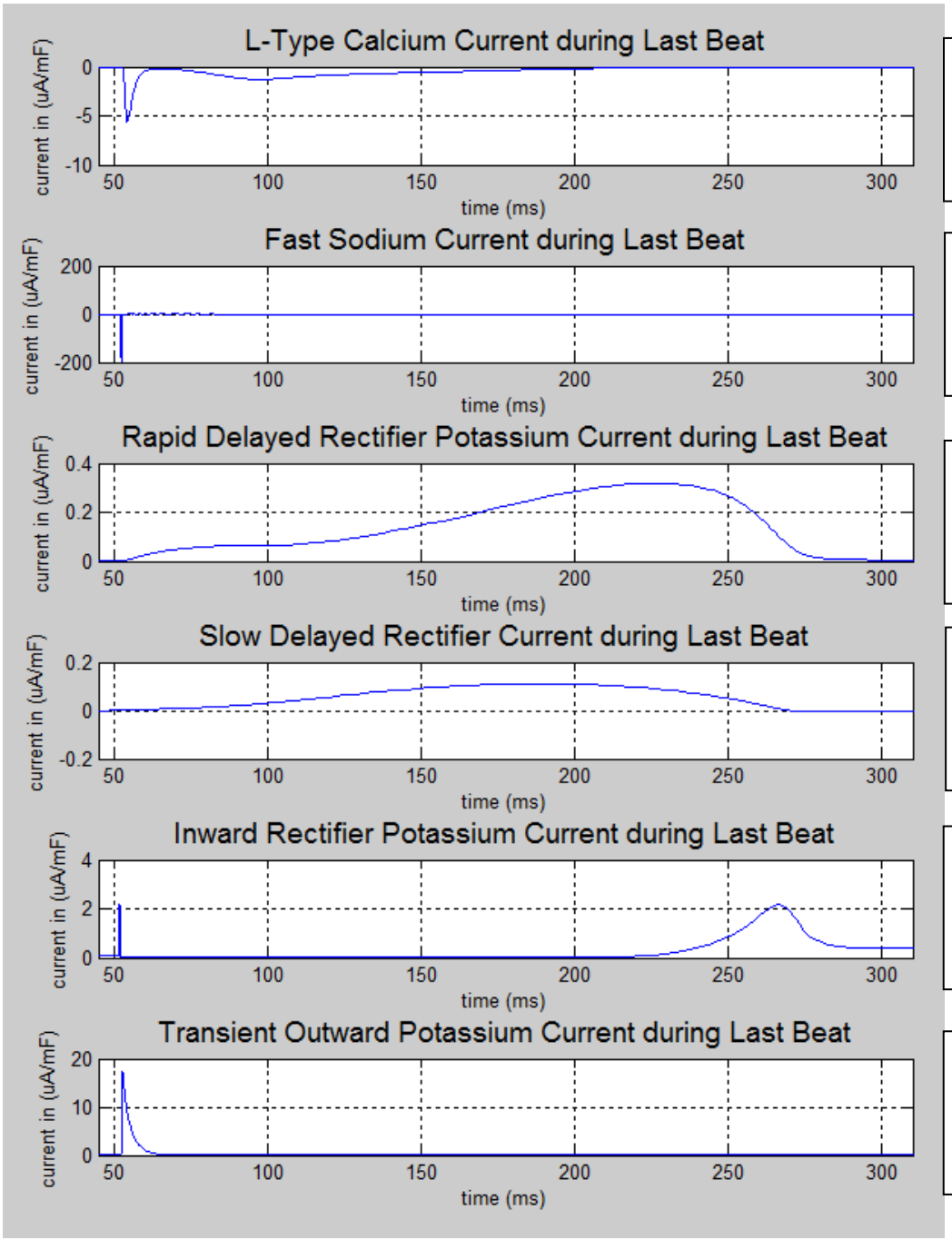
Problem 1.3:

```
% define the currents
ical = currents.ical;    % L-type calcium current
ina = currents.INa;      % fast sodium current
ikr = currents.ikr;      % rapid delayed rectifier potassium current
iks = currents.iks;      % slow delayed rectifier potassium current
ik1 = currents.IK1;      % inward rectifier potassium current
ito = currents.Ito;      % transient outward potassium

t_a=31288;               %shorten indices of starting time for the last beat
t_b=31565;               %shorten indices of ending time for the last beat
t2plotShort=t(t_a:t_b,1)'-t(t_a);   %shorten row vector of times from the last beat
v2plotShort=v(t_a:t_b,1)';          %shorten row vector of voltages from the last beat
as a reference for the phases

figure;
plot(t2plotShort,v2plotShort);  xlim([45,310]);
grid on;  title('Voltage vs time as reference for analysis of phases','fontsize',14);
xlabel('time (ms)'); ylabel('Voltage (mV)');

figure;
subplot(6,1,1);
plot(t2plotShort,ical(t_a:t_b,1)');  xlim([45,310]);
grid on;  title('L-Type Calcium Current during Last Beat','fontsize',14);
xlabel('time (ms)'); ylabel('current in (uA/mF)');

subplot(6,1,2);
plot(t2plotShort,ina(t_a:t_b,1)');   xlim([45,310]);
grid on;  title('Fast Sodium Current during Last Beat','fontsize',14);  xlabel('time
(ms)'); ylabel('current in (uA/mF)');

subplot(6,1,3);
plot(t2plotShort,ikr(t_a:t_b,1)');   xlim([45,310]);
grid on;  title('Rapid Delayed Rectifier Potassium Current during Last
Beat','fontsize',14);  xlabel('time (ms)'); ylabel('current in (uA/mF)');

subplot(6,1,4);
plot(t2plotShort,iks(t_a:t_b,1)');   xlim([45,310]);
grid on;  title('Slow Delayed Rectifier Current during Last Beat','fontsize',14);
xlabel('time (ms)'); ylabel('current in (uA/mF)');

subplot(6,1,5);
plot(t2plotShort,ik1(t_a:t_b,1)');   xlim([45,310]);
grid on;  title('Inward Rectifier Potassium Current during Last Beat','fontsize',14);
xlabel('time (ms)'); ylabel('current in (uA/mF)');

subplot(6,1,6);
plot(t2plotShort,ito(t_a:t_b,1)');   xlim([45,310]);
grid on;  title('Transient Outward Potassium Current during Last Beat','fontsize',14);
xlabel('time (ms)'); ylabel('current in (uA/mF)');
```

The lab manual stated: "Use the same x-axis scale for each plot, but also make sure your plot clearly shows the relevant active period for each current. You do not have to display the entire duration of the AP." However, since each current's action is located in a different section of the AP's overall time course, it is hard to use the same range for the x-axis and not show the entire AP. Because of this, the entire duration of the AP is shown for each current, and the conglomerate is shown for reference. This way a visual comparison between a specific current and the reference may yield information about what contribution a specific channel is adding to the sum.



Figures 2 & 3:
Fig 2 (left) The time-course of the cardiac AP for reference.
Fig 3 (left/below) The current contribution of individual Ion Channels



- **Depolarizing** or Repolarizing Current?
- Primarily **inward** or outward current?
- Phases Affected: 1a, 1b, **2**, 3, 4
- Phases Less Affected: **1a**, 1b, 2, **3, 4**

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- Phases Less Affected: **1a,** 1b, **2, 3, 4**

Depolarizing current is a positive ion entering the cell (negative current), repolarizing is it leaving cell (positive current).

Problem 1.4

```
%Calculate APD_90
Y=diff(v2plotShort)./diff(t2plotShort);  %first derivative of voltage
dvdt_max=max(Y);
dvdt_max_index=find(Y==dvdt_max);

V_rest=v2plotShort(1);
[V_max,V_max_index]=max(v2plotShort);

v_90=V_max-0.9*(V_max-V_rest);
v_90_index=find(v2plotShort>=v_90,1,'last');

APD_90_control=t2plot(v_90_index)-t2plot(dvdt_max_index);

prob_3_control(length(prob_3_control)+1)=APD_90_control;
```

Problem 1.4 Results:

APD_{90}	209.2085 ms

Table 2:
APD_{90} results from problem 1.4

Problem 2.1 (a):

```
R=8314;
T=37+273;
F=96485;
z_Na=1;
z_K=1;
Xo_Na=140;
Xi_Na=10;
Xo_K=4.5;
Xi_K=140;

E_Na=(R*T/(z_Na*F))*log(Xo_Na/Xi_Na);    %Nernst Potential for Sodium;
E_K=(R*T/(z_K*F))*log(Xo_K/Xi_K);        %Nernst Potential for Potassium;
```

2.1 (a) Results

E_k (Nernst Potential for potassium)	-91.8254 mV
E_{Na} (Nernst Potential for sodium)	70.4954mV

Table 3:
Nernst Potential results for both potassium and sodium from problem 2.1

Problem 2.1 (b) & (c):

```
Vm=-100:50;                                %membrane potential from -100 to 50

drivingForce_Na=Vm-E_Na;                   %electrochemical Driving Force for Na
drivingForce_K=Vm-E_K;                     %electrochemical Driving Force for K

figure; hold all;
plot(Vm,drivingForce_Na); grid on;
grid on;
plot(Vm,drivingForce_K);  title('Electrochemical Driving Force vs. Membrane
Potential','fontsize',12);
legend('Na','K');  xlabel('membrane Potential (mV)'); ylabel('electro chemical Driving
Force (mV)');
```

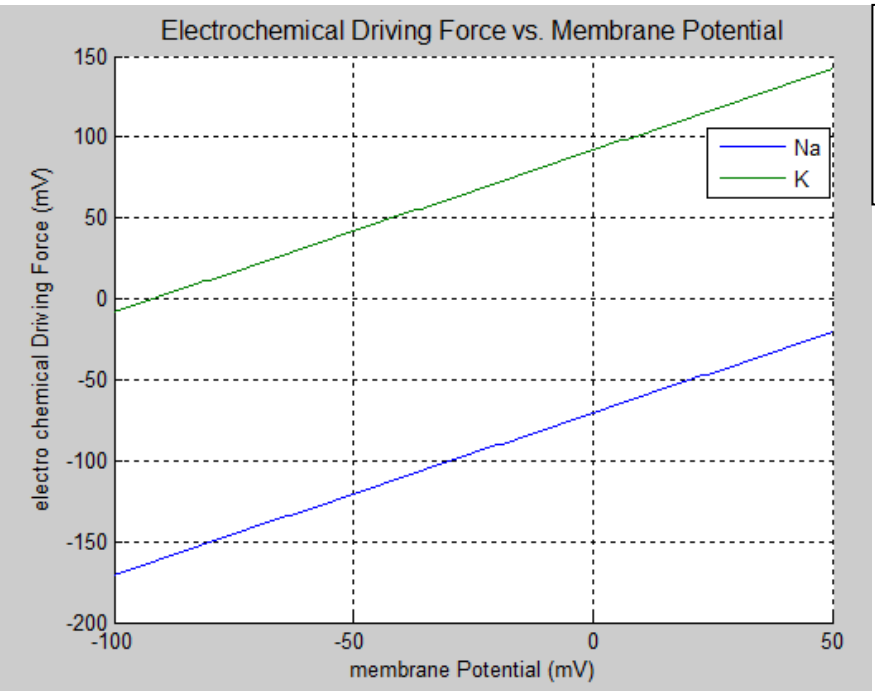


Figure 4:
Comparison of electrochemical driving force (as a fxn of membrane voltage) for both sodium and potassium

Question 2.1 (b)

At membrane voltage=0-20mV range, the driving force for potassium is positive, and therefore positively charged potassium ions tend to flow out of the cell. For the same voltage range, the driving force for sodium is negative, and therefore the positively charged sodium ions tend to flow into the cell.

Part (c):

```
Xo_K=4;
E_K_norm=(R*T/(z_K*F))*log(Xo_K/Xi_K);   %Normal Nernst Potential for Potassium;
DrivingForce_K_norm=Vm-E_K_norm;
Xo_K=7.5;
E_K_hL=(R*T/(z_K*F))*log(Xo_K/Xi_K);     %abnormal Nernst Potential for Potassium with
HyperKalemia;
DrivingForce_K_hL=Vm-E_K_hL;

figure; hold all;
plot(Vm,DrivingForce_K_norm); grid on;
plot(Vm,DrivingForce_K_hL);title('Electrochemical Driving Force vs. Membrane Potential
compared for Normal and Elevated Extracellular [K]','fontsize',12);
legend('Normal [K]ext=4','Elevated [K]ext=7.5 with hyperKalemia');  xlabel('membrane
Potential (mV)'); ylabel('electro chemical Driving Force (mV)');
```

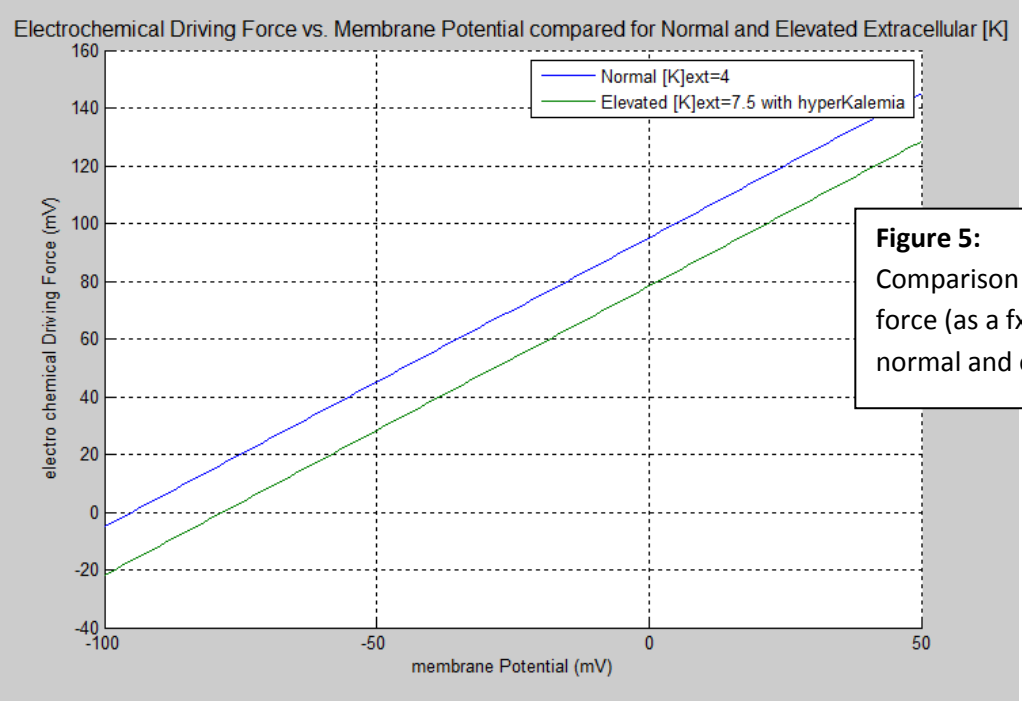


Figure 5:
Comparison of electrochemical driving force (as a fxn of membrane voltage) normal and elevated levels of potassium

Question 2.1 (c)

Membrane potential is primarily a result of a large intracellular concentration of potassium relative to a small extracellular concentration. In hyperkalemia, the extracellular concentration is elevated, and disturbs the basis of membrane potential. If extracellular potassium concentration is elevated, the magnitude of the concentration gradient decreases and therefore the driving force for potassium to move across the membrane decreases as well. At the onset of an AP, the membrane potential plays a large role in determining the number of activated Na channels, and therefore the rate and height of the initial depolarization. In hyperkalemia, the resting potential becomes less negative, and the percentage of depolarizing sodium channels will decrease. The maximum depolarizing voltage decreases as a result. This means for a propagation, the QRS complex must elongate, which can cause arrhythmia and threaten cardiac function. (source: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1413606/)

Problem 2.2

```
V=[-90,-15,0,10,20];

alpha=zeros(1,length(V));
beta=zeros(1,length(V));

for i=1:length(V)
alpha(i)=25*exp((V(i)-40)/10)/(1+exp((V(i)-40)/10));
beta(i)=25*exp((-(V(i)+90)/10))/(1+exp(-(V(i)+90)/10));
end
```

Table 4:
Values of rates going from open to closed (beta) and closed to open (alpha) at different membrane voltages indicative of different phases of the cardiac AP

2.2 (a) Results

Membrane Voltage (mV)	-90	-15	0	10	20
Alpha(V)	0.0001	0.1018	0.4497	1.1856	2.9801
Beta(V)	12.500	0.0138	0.0031	0.0011	0.0004
Ratio (Alpha/Beta)	0.000008	7.376812	145.0645	1077.818	7450.25
Ratio (Beta/Alpha)	125000	0.13556	0.006893	0.000928	0.000134

2.2 (a) Answer:

At resting level (-90mV), the majority of the channels will be in a closed state. This is shown by a dominating value of beta 5 orders of magnitude larger than alpha. If the voltage is held at plateau potential (between 0-20mV), the majority of the channels will be open. This is shown by a dominating value of alpha 3-4 orders of magnitude larger than beta. For quantitative ratios, see the chart above.

2.2 (b) Answer:

The more open the channel, the more current flows… the more current that flows, the larger the magnitude of dv/dt. This means larger currents will produce more rapid changes in membrane potential. During phase 2, when membrane voltage is around 0mV, the channel action is dominated by alpha. See the table above. This means the channels will be overwhelmingly open. When the channels are open the ions will flow in the direction that moves the membrane potential V_m toward E_k. In this case that is outward, given at V_m=0mV, E_k is more negative at around -90mV. Membrane potential is relative and by definition negative on the inside. Therefore depolarization is a net inward flow of positive ions, & repolarization a net outward flow of positive ions. During phase 2, membrane voltage is not at rest, it must repolarize/rectify itself to resting potential. An outward flow of potassium ions accomplishes this repolarization via open potassium channels shown by a large alpha/beta ratio for V_m~0mV.

In phase 4, at resting potential (~-85mV) the channel action is dominated by beta. See the table above. This means the channels will be overwhelmingly closed. Because of this, potassium will not flow

through these channels, and therefore play little role in affecting membrane voltage V_m. This is why phase 4 holds a constant membrane voltage, because there is no flow of ions and no current to change the voltage. The membrane potential during phase 4 has already been rectified during phases 2 and 3 and must stay at steady state. This means a continued outflow of rectifying potassium ions is not needed and the channels close, shown by a dominating Beta.

One can look at the explanation from a voltage perspective as well. Since K channel is voltage gated, a negative voltage will not do much to activate it. At resting potential (~-85mv) the voltage gated channel is dominantly closed expressed by larger Beta in phase 4. But if V_m increases to large positive voltages (during an AP) then the voltage gated channel will open (represented by larger Alpha) as in phase 2.

Problem 3.1:

Parameter:	Dv/dt_{max}	$[Ca^{2+}]_{int.\ max}$	V_{max}	V_{rest}	APD_{90}
Control:	272.6017	0.0006	37.9287	-85.7242	209.2085
Reduced Na channel Density:	137.0025	0.0003	14.3650	-85.7818	244.1703
Ratio Reduced/Control	0.5026	0.4729	0.3787	1.0007	1.1671

Table 5: Cardiac AP parameters with a 75% reduction in Na channel density

The reduced Na channel density leads to a decrease in dv/dt_{max} or in other words a decrease in the rate at which the initial depolarization occurs by about 50%. This affects the amount of Ca2+ that enters, significantly decreasing the maximum intracellular concentration of Ca^{2+} by about 50%. The maximum voltage during the action potential surprisingly does not occur after initial depolarization, but instead on the hump between phases 1 & 2. It increases negligibly, but the local maximum voltage near the beginning of the AP is less than the control. APD_{90} is increased by about 17%.

Morphology of the AP changes, as the reduced Na AP is broader (has a longer time course). The AP's max V is no longer after initial depolarization of phase 0, but instead a hump of depolarization after phase 1 before phase 2.

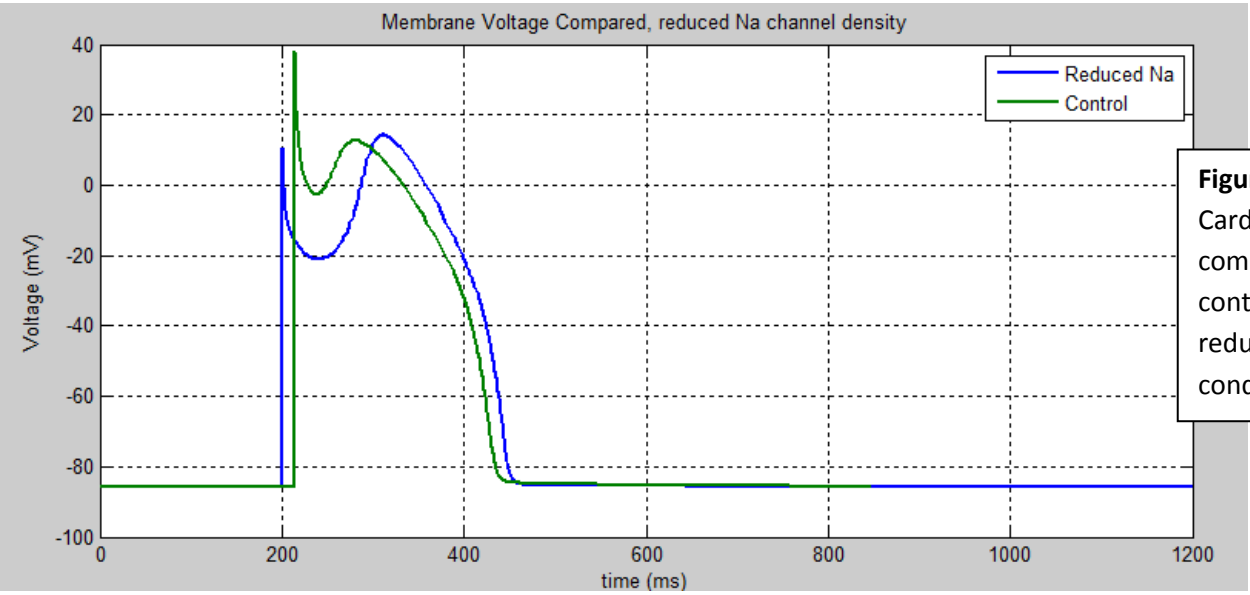


Figure 6: Cardiac APs compared for control and reduced INa condition

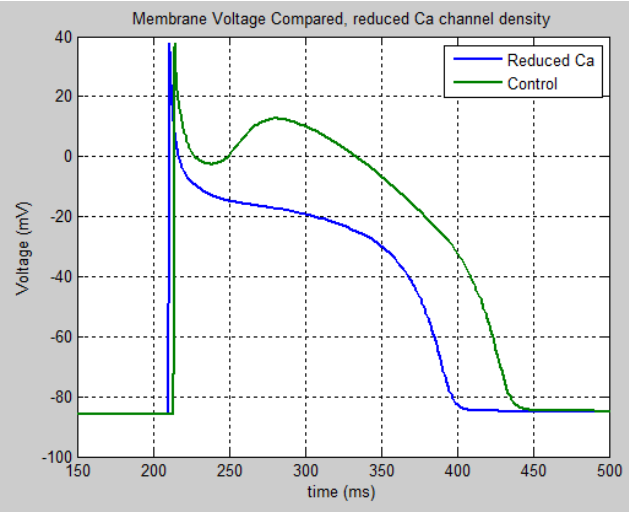
Problem 3.2:

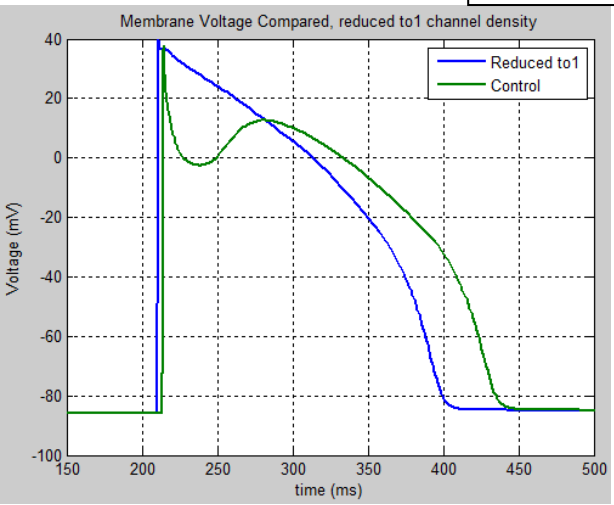
Currents affecting phase 1 notch are Ca2+ and to1

Table 6:
APD_{90} results for reduced Ca and to1 channel densities

Channel Setup	APD_{90}	Ratio Experiment/Control
Control	209.2085	1
Reduced Ca Density	181.1998	0.8661
Reduced to1 Density	183.3172	0.8762

Figures 7 & 8:
Cardiac APs compared for control and reduced ICa & Ito1 conditions





The 75% reduced Ca^{2+} channel density caused ~13% decrease in APD^{90}. The 75% reduced to1 channel density caused ~12% decrease in APD^{90}.

Problem 3.3:

75% reduction in IK1 density affected phase 3 of the AP, slowing the rapid repolarization during phase 3 so that it almost matched the rate in phase 2. This slowing caused APD_{90} to increase by ~32%.

Channel Setup	APD_{90}	Ratio Experiment/Control
Control	209.2085	1
Reduced k1 Density	275.7204	1.3179

Table 7:
APD_{90} results for reduced k1 channel densities

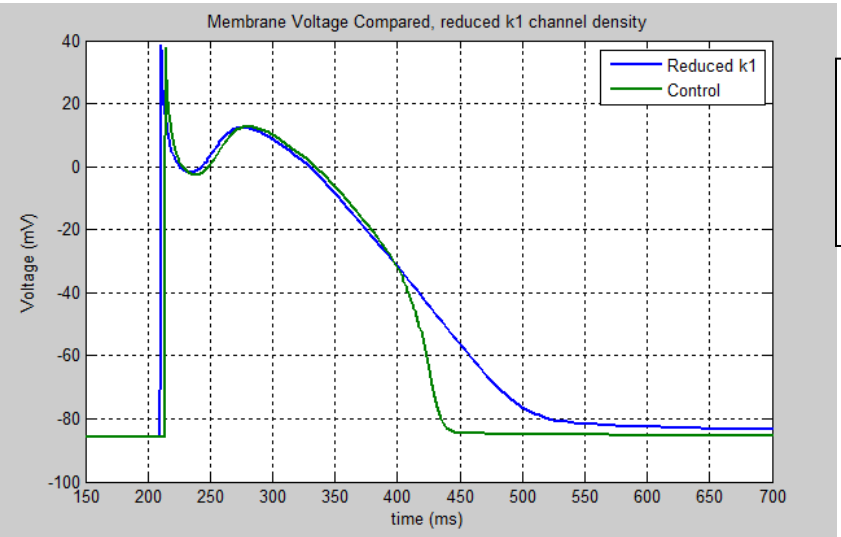


Figure 9:
Cardiac APs compared for control and reduced Ik1

Problem 3.4:

Table 8:
Cardiac AP parameters for control, reduced IKs, & reduced IKr

Parameter:	Dv/dt_{max}	$[Ca^{2+}]_{int.\ max}$	V_{max}	V_{rest}	APD_{90}
Control:	272.6017	0.0006	37.9287	-85.7242	209.2085
Reduced Ks channel Density (relevant to LQT type 1):	272.8254	0.0006	37.9290	-85.7818	230.0726
Reduced Kr channel Density (relevant to LQT type 2):	272.8248	0.0006	37.9287	-85.7818	262.4463
Ratio Reduced Ks/Control:	1.0008	1.0000	1.0000	1.0007	1.0997
Ratio Reduced Kr/Control:	1.0008	1.0000	1.0000	1.0007	1.2545

Neither a 75% reduction in Kr or Ks channel density produced a noticeable change in 4 of the 5 parameters above. The AP phases that were affected were phases 2 and 3, where none of the parameters tell much of a story. APD_{90} however increased in both reduction. For reduced IKr, the APD_{90} increased almost 10% and for reduced IKs, the APD_{90} increased over 25%. For this reason, I would venture to say LQT type 2 results in a more sever phenotype. Being linked with a reduction in IKr has a change in APD_{90} that is over 2.5 times as large as the APD_{90} change resulting from IKs reduction. A 25% change in APD_{90} could lead to threatening arrhythmias and other cardiac problems.

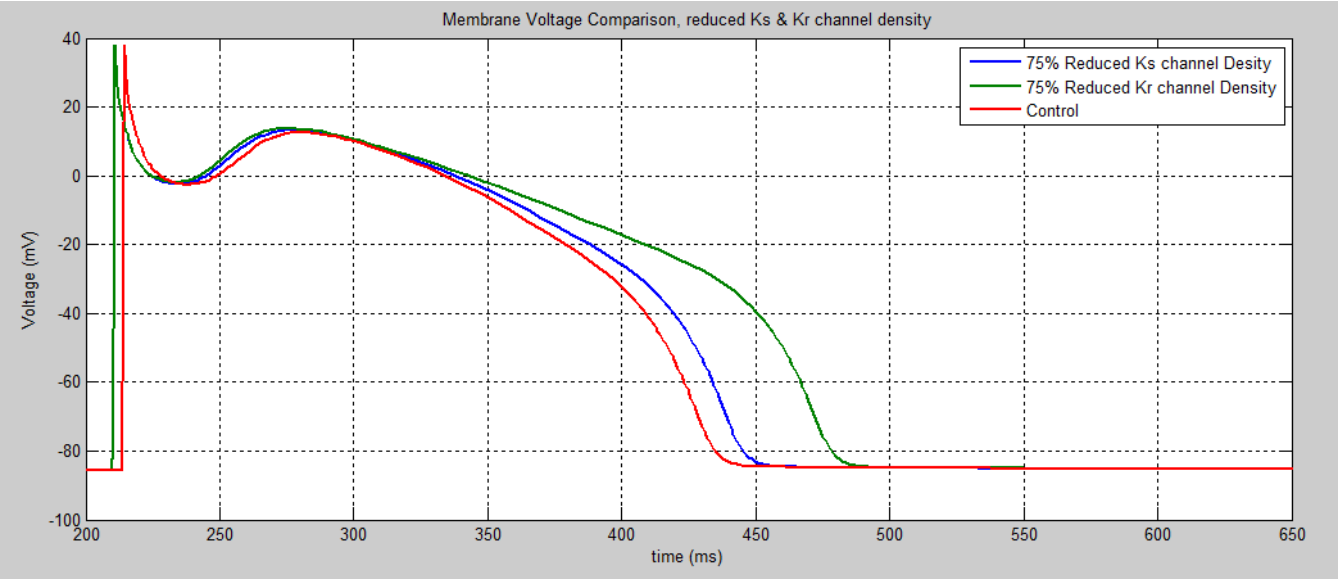


Figure 10:
Cardiac APs compared for control and reduced Iks & IKr

Discussants: Mathew Everret, Lauren Bedell, Maeve Marie, Paras Vora