Computational Cardiac Electrophysiology Lab: 
The Luo-Rudy 1 model

In this lab, you’ll explore the dynamics of a particular ionic model of the cardiac action potential - the so-called Luo-Rudy 1 model.\(^1\) The model (shown schematically below) consists of six transmembrane currents: a sodium current ($I_{Na}$), a calcium current ($I_{Ca}$), three distinct potassium currents ($I_{K}$, $I_{K1}$, and $I_{Kp}$), and a non-specific background current ($I_b$). You will learn the role of these different currents in shaping the action potential and investigate the effects of blocking them.

![Figure 1: Schematic illustration of LR1 model.](image)

1. Role of individual currents

\(a\) The sodium current
Run the LR1 in its default configuration (type “LR1(1,’blue’)” in your matlab command window). The first argument to the function sets the figure window number, the second argument sets the color of the traces. Vary these as you see fit in the remainder of the lab to facilitate comparison between different simulations.

At what phase of the action potential is $I_{Na}$ on?

Recall from yesterday’s lecture that $dV/dt = -I_{ion}/C_m$. What is the effect of a large, negative current on the rate of change of $V$?

What do you expect will happen if the sodium channel is blocked completely? Try (multiply the sodium conductance by zero in line 11 and re-run LR1, e.g., “LR1(1,’red’)”)! Were you right? Tetrodotoxin (TTX) is a highly specific sodium channel blocker found in pufferfish (fugu). Would you eat fugu?

\(^1\)Luo & Rudy, Circ Res 68:1501, 1991
Try to find the critical sodium conductance needed to evoke an action potential. You’ll notice that action potentials evoked at values of \( g_{\text{Na}} \) just above threshold are very similar to those at the default \( g_{\text{Na}} \)-value. This is the reason why action potential generation is called an all-or-none phenomenon.

b) The calcium current
Change the sodium conductance back to its default value (23.0) and run the model again. The calcium current is inward (negative), as is the sodium current, but the calcium current has very different dynamics. What do you think is the role of \( I_{\text{Ca}} \) in terms of the shape of the action potential? Try halving the calcium conductance (line 13). How does this change the action potential?

c) The time-dependent potassium current
\( I_{\text{K}} \) is outward (positive). What happens if \( g_{\text{K}} \) is set to double its default value? To half its default value?

d) The time-independent potassium current
During what phases of the action potential is \( I_{\text{K}_1} \) on?

What you think will happen if you decrease \( g_{\text{K}_1} \)? (Try 20% of its normal value).

Try setting \( g_{\text{K}_1} \) to zero and run the simulation for longer time (increase \( t_{\text{end}} \) in line 30 to 3000 ms). What just happened? Cardiac pacemaker cells are cells that beat spontaneously. They have little \( I_{\text{K}_1} \) compared to ventricular cells.

e) Optional: gating variable dynamics
Try to understand the dynamics of \( I_{\text{Na}} \), \( I_{\text{Ca}} \), \( I_{\text{K}} \), and \( I_{\text{K}_1} \) during the action potential by plotting and examining the time course of their gating variables (activation and inactivation). Do you see how the gating dynamics emerge from the activation/inactivation curves \( x_{\infty} \) and \( \tau_x \)?

2. Early afterdepolarizations
Early afterdepolarizations are additional depolarizations of the cell membrane that occur prior to full repolarization (see figure). As discussed in the lecture yesterday, early afterdepolarizations may trigger cardiac arrhythmias.

Experimentally, early afterdepolarizations typically occur upon administration of drugs that either increase the calcium current or drugs that block the time-dependent potassium current. The latter type is of particular concern because one of the channel proteins that give rise to the time-dependent potassium current is highly susceptible to drug block. Therefore, all new drugs, cardiac
and others, are screened to see if they prolong repolarization before getting FDA approval.

Using the LR1 model, try to see if you can simulate early afterdepolarizations by blocking $I_K$ and/or boosting $I_{Ca}$. Which ionic current generates the early afterdepolarization?

3. Repolarization alternans
Repolarization alternans, where there is a long-short alternating pattern in the duration of the action potential, is another example of pro-arrhythmic electrodynamics. The original LR1 model does not exhibit alternans with rapid pacing – this is a flaw of the model as real ventricular cells do. However, by changing a few parameters, the model is capable of showing alternans. This slightly modified model has been implemented in LR1_alternans.m.

a) Ionic mechanism of alternans
Run LR1_alternans.m (it takes the same plotting parameters as LR1.m). The cell is now paced at a relatively rapid pace (195 ms). Is there alternans? What is the relationship between the diastolic interval (i.e., the resting interval between action potentials) and the action potential duration?

What is the relative size of $I_{Ca}$ during the long action potential vs. the short one? Of $I_K$? Do these changes agree with what you found in Problem 1, regarding the roles of $I_{Ca}$ and $I_K$ on action potential duration?
b) Alternans control
The program LR1_ctrl.m contains the following alternans control algorithm:

\[
T_{n+1} = \begin{cases} 
T^* & \text{for } \Delta T_{n+1} > 0, \\
T^* + \Delta T_{n+1} & \text{for } \Delta T_{n+1} \leq 0,
\end{cases}
\]  

with

\[
\Delta T_{n+1} = \frac{\gamma}{2} [\text{APD}_{n+1} - \text{APD}_n],
\]

where \( \gamma \) is the feedback gain, \( T \) is the pacing period (\( T_n \) is the period of the \( n \)th action potential), \( T^* \) is the unperturbed pacing period, and APD is the action potential duration.

This algorithm is designed to shorten long diastolic intervals by shortening the pacing period when a short action potential has followed a long one.

Run the program. Did it work? Do you understand why? What happens when you change the control parameter \( \gamma \) (line 35)?