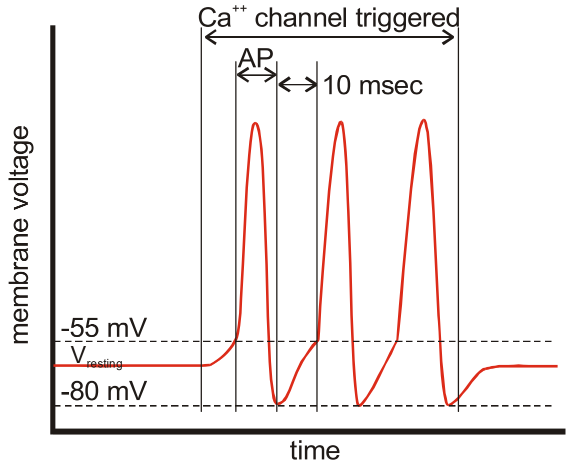
Quantitative Physiology I / Molecular and Cellular Systems; BMEN E4001x
HW4: Channels and potentials,
Due Nov. 12, 2025, 11:00PM

1) Design of an action potential burst cell (20 points)

Assume your lab has cells with excitable membranes, equipped with voltage sensitive Na^+ and K^+ channels sufficient to produce action potentials. Your task is to modify these cells such that they produce a train of action potentials at set time intervals on demand. You plan to do this by introducing a new Ca^{++} channel. When triggered, these channels increase Ca^{++} conductance, altering the cells' electrical properties.

Your mission in this problem is to specify the conductance of these Ca^{++} channels that would induce a pulse train in which action potentials start every 20 ms.



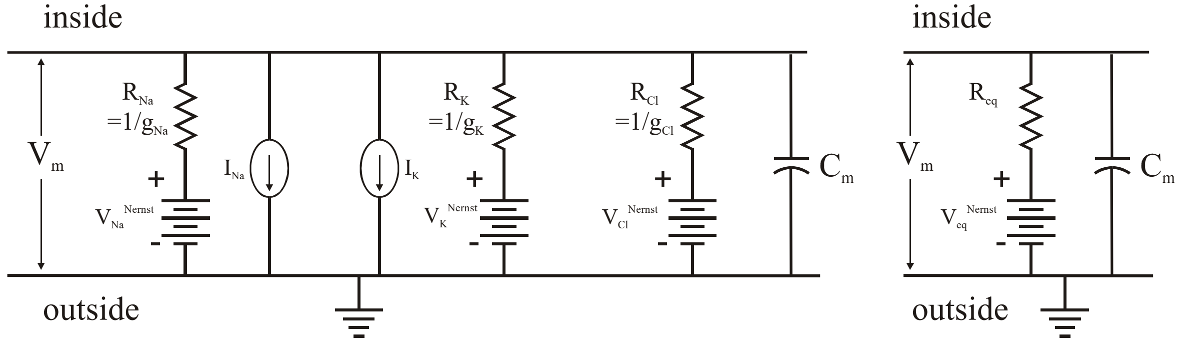
Assume:

ion	internal conc. (mM)	external conc. (mM)	pump rate (absolute value) ($\mu A/cm^2$)	V^{Nernst} (mV)	conductance (S/cm^2)
Na^+	15	145	1.356	60.605 mV	1.0×10^{-5}
K^+	120	5	0.9898	-84.898 mV	1.0×10^{-4}
Cl^-	7	116	--	-75.00 mV	2.0×10^{-5}
Ca^{++}	1×10^{-4}	1.2	--	(to be calculated)	0 when inactive, for you to specify when active

- Membrane capacitance is 1 $\mu F/cm^2$.
- The Ca^{++} channels allow passage of only Ca^{++} ions during the trigger signal.
- Note that the Ca^{++} ion has two positive charges.
- Each action potential:
  - is started when the membrane voltage increases to <u>–55 mV</u>,
  - lasts <u>10 ms</u>; the goal is to design a <u>10 ms</u> period between the end of one action potential and beginning of the next,
  - terminates with instantaneous closure of the repolarizing K^+ channels. Membrane voltage at this point = <u>–80 mV</u> (this is a simplifying assumption), and
  - is mediated by channels whose conductance overwhelms the resting conductance during the action potential but are completely off outside of the 10 ms action potential.
- Constants and units:
  - T = 310 K;
  - 1 Siemens = 1 Amp / Volt
  - 1 Volt = 1 J / C = 1 N*m/C; (C = Coulombs)
  - 1 Amp = 1 C/sec
  - 1 F * 1 Ω = 1 sec; 1 S = 1 1/Ω ; 1Ω=1V/A

Part A - Electrical Equivalence (5 points)

1.1) Consider the membrane to be modeled as the pump-leak model with a capacitor element. Derive that, in terms of the electrical equivalence circuit, the right schematic is equivalent to the left circuit, with the specified values of equivalent resistance and voltage source.



$$R_{eq} = \left(\frac{1}{R_{Na}} + \frac{1}{R_K} + \frac{1}{R_{Cl}} \right)^{-1} \text{ (or alternatively) } g_{eq} = g_{Cl} + g_K + g_{Na}$$

$$V_{eq}^{Nernst} = \frac{-I_{Na} - I_K + g_{Na}V_{Na}^{Nernst} + g_K V_K^{Nernst} + g_{Cl}V_{Cl}^{Nernst}}{g_{Na} + g_K + g_{Cl}}$$

1.2) What is the resting potential for this system?

Part B – Design of Electrical Response (15 points)

Now consider the membrane with channels that provide a Ca^{++} conductance of g_{Ca}. (That is, consider the system with the channels triggered to be open).

1.3) Expand the model from Part 1 to include the new Ca^{++} channel. Provide an expression for a new resting potential as a function that includes g_{Ca}. Assume that the membrane is not excitable, so approaching this new potential does not initiate an action potential.

1.4) For an experiment in which the membrane voltage is first clamped to -80 mV and then released, provide an equation describing membrane voltage as a function of time. Provide numbers for key voltages. As in part 1.3, assume here that the membrane is not excitable.

1.5) Provide an expression for how long it takes after release (unclamping) for the membrane voltage to reach -55 mV. That is, for an excitable membrane, how long will it take before a new action potential is initiated?

1.6) What Ca^{++} conductance is needed to provide a 10 ms gap between the hyperpolarization phase and initiation of a new action potential?

Solution

Part A - Electrical Equivalence (5 points)

1.1) There are several approaches to this. Kirchhoff's current law, applied to the inside or outside spaces, is perhaps the most straightforward. Thevenin-Norton equivalence transformations are also relevant. Note that in the original setup, the resistors are not exactly in parallel with each other. There is a voltage source in series with each resistor, so one can't just state that the resistors are in parallel.

1.2) Evaluate V_{eq}^{Nernst} with the numbers given in the table. Note that the sign of the Na current is positive, while the sign of the K current is negative. With these, V_{eq}^{Nernst} = -75 mV.

Part B – Design of Electrical Response (15 points)

1.3) The new channel looks like the Na^+, K^+, and Cl^- channels, a resistor in series with a voltage supply. Either reworking the circuit or just using the existing result as a template,

$$V_{eq}^{Nernst} = \frac{-I_{Na} - I_K + g_{Na}V_{Na}^{Nernst} + g_K V_K^{Nernst} + g_{Cl}V_{Cl}^{Nernst} + g_{Ca}V_{Ca}^{Nernst}}{g_{Na} + g_K + g_{Cl} + g_{Ca}}$$

$$g_{eq} = g_{Cl} + g_K + g_{Na} + g_{Ca}$$

You'll thus need the Nernst potential for Ca^{++}, V_{Ca}^{Nernst}=125.45 mV

1.4) This is a classic RC circuit, starting at -80 mV but then going to the result identified in 1c,

$$V(t) = (V_{eq}^{Nernst} + 80mV)*(1 - \exp(-t/(R_{eq}C_m))) - 80mV$$

or

$$V(t) = (V_{eq}^{Nernst} + 80mV)*(1 - \exp(-t*(g_{eq}/C_m))) - 80mV$$

1.5) Set V(t)=-55 mV in the result of 1d, invert the equation.

$$t = -R_{eq}C_m * \ln\left(1 - \frac{25mV}{V_{eq}^{Nernst} + 80mV}\right) = -\frac{C_m}{g_{eq}} * \ln\left(1 - \frac{25mV}{V_{eq}^{Nernst} + 80mV}\right)$$

1.6) The equation of 1.5 is a little complicated to solve as g_{Ca} affects V_{eq}^{Nernst}. Some sort of numerical approach, including Excel or Matlab, is quite handy to solve the results of 1.3 and 1.5 simultaneously.

g_{Ca}=2.037e-5 S/cm^2

Kirchhoff's current law, applied to inside of cell
→ positive current is flow of positive charges from inside to outside

membrane model

$$① \quad \underbrace{\sum_i (V_m - V_i^{Nernst}) g_i}_{\text{channels}} + \underbrace{\sum_i I_i}_{\text{pumps}} + C_m \frac{dV_m}{dt} = 0$$

$$② \quad \sum_i V_m g_i - \sum V_i^{Nernst} g_i + \sum_i I_i + C_m \frac{dV_m}{dt} = 0$$

$$③ \quad \underbrace{V_m \sum_i g_i}_{A} \underbrace{- \sum V_i^{Nernst} g_i + \sum_i I_i}_{B} + \underbrace{C_m \frac{dV_m}{dt}}_{C} = 0$$

RC circuit

$$④ \quad (V_m - V_{eq}^{Nernst}) g_{eq} + C_m \frac{dV_m}{dt} = 0$$

$$⑤ \quad \underbrace{V_m g_{eq}}_{A} \underbrace{- V_{eq}^{Nernst} g_{eq}}_{B} + \underbrace{C_m \frac{dV_m}{dt}}_{C} = 0$$

Goal is to relate ③ to ⑤

→ V_m only appears in first term, A. so $g_{eq} = \sum_i g_i$

→ C_m only appears in the last terms and must be equal.
They are indeed equal, nothing else to do

→ Thus, the middle terms, B, are equal.

$$-V_{eq}^{Nernst} g_{eq} = -\sum V_i^{Nernst} g_i + \sum_i I_i$$

divide by g_{eq}, change sign

$$V_{eq}^{Nernst} = \frac{-\sum_i I_i + \sum_i V_i^{Nernst} g_i}{g_{eq}}$$

alternatively, set the current going into the capacitor to be equal in both setups.

$$V_m \sum_i g_i - \sum_i V_i^{Nernst} g_i + \sum_i I_i = V_m g_{eq} - V_{eq}^{Nernst} g_{eq}$$

The way to make this work is the same. All terms with V_m should be equal, so

$$g_{eq} = \sum_i g_i$$

$$V_{eq} = \frac{\sum_i V_i^{Nernst} g_i - \sum_i I_i}{g_{eq}}$$

2) Rescue a cell (10 points)

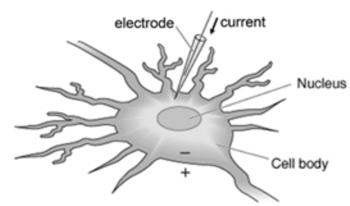
This Question focuses on the same cell as Question 1, with the parameters listed above. In addition, assume the cell has a surface area of 1000 μm^2 = 1 x 10^{-5} cm^2.

2.1) At time t=0, the cell is subjected to ouabain, a toxin that selectively blocks the Na^+/K^+ pump. What is the cell's new resting potential?

$$V_{eq,ouabain}^{Nernst} = \frac{0 * (-I_{Na} - I_K) + g_{Na}V_{Na}^{Nernst} + g_K V_K^{Nernst} + g_{Cl}V_{Cl}^{Nernst}}{g_{Na} + g_K + g_{Cl}}$$

= -72.182 mV

2.2) You want to offset the effect of ouabain on membrane voltage by inserting a transmembrane electrode into the affected cell. Update the expressions in HW4Q1 for R_{eq} and V_{eq}^{Nernst} to include the effect of the electrode. Consider a flow of positive charges into the cell as a positive current. *This is opposite for what we assigned for channels and pumps.*



This question builds off the circuit model of the cell membrane in HW4. The resting potential for the membrane (corresponding to V_{eq}^{Nernst}) becomes

$$V_{eq,clamp}^{Nernst} = \frac{-I_{Na} - I_K + I_{elec} + g_{Na}V_{Na}^{Nernst} + g_K V_K^{Nernst} + g_{Cl}V_{Cl}^{Nernst}}{g_{Na} + g_K + g_{Cl}}$$

$R_{eq}=(1/R_{Na}+1/R_K+1/R_{Cl})^{-1}$

OK if the $g_{Na}*V_{Na}^{Nernst}$ and g_{Na} terms are left out, since the toxin blocks the Na^+ channel.

2.3) What electrode current (in Amperes) is needed to maintain the membrane voltage at -75 mV? Remember, ouabain is still present, inhibiting the pump.

(in V and A/cm^2)

$$-.075 = \frac{0 + I_{elec} + (1e-5)*(0.0606) + (1e-4)*(-0.0849) + (2e-5)*(-0.075)}{1e-5 + 1e-4 + 2e-5}$$

I_{elec} =-.366 μA/cm^2.

For whole cell of 1000 μm^2, I_{elec} = -3.66e-12 A