The Resting Potential II

Review

- Nernst equilibrium
  - Nernst equation
  - Nernst equilibrium potential
- establishment of osmotic balance between intracellular and extracellular compartments
  - need impermeant extracellular ion to balance osmotic effect of impermeant intracellular molecules
- Donnan equilibrium
  - distribution of two permeant ions so that they share the same equilibrium potential
- portrait of hypothetical cell at equilibrium
  - $E_m = E_k = E_c$
- Deviation of real neurons from equilibrium conditions
  - under equilibrium conditions, there would be no net transmembrane ionic fluxes
  - in real neurons, both $Na^+$ and $K^+$ can and do leak across membrane
    - thus, resting neurons are not at equilibrium
  - $Na^+/K^+$ pump maintains concentrations, compensating for leaks
  - Cell is in steady-state, not equilibrium
    - cell uses energy to maintain ion concentrations

The battle for control of the membrane potential

- if the membrane potential ($E_m$) equals Nernst potential for an ion ($E_{ion}$), there will be no net flux of that ion across the membrane
  - illustration:
• vary membrane potential of cell \( (E_m) \) while measuring flux of 
  \( K^+ \) when \( E_m = E_k \), no flux
  when \( E_m \) is more negative than \( E_k \), influx of \( K^+ \) (\( K^+ \) flows into 
  cell)
  influx of \( K^+ \) makes the membrane potential less negative = 
  depolarization
  when \( E_m \) is more positive than \( E_k \), efflux of \( K^+ \) (\( K^+ \) flows out of 
  cell)
  efflux of \( K^+ \) makes the membrane potential more negative = 
  hyperpolarization
  o thus, *when the the equilibrium potential for a permeant ion differs 
    from the membrane potential, that ion will tend to flow across 
    membrane so as to draw the membrane potential closer to its 
    equilibrium potential*

  • qualitative state of \( K^+ \) and \( Na^+ \) under steady-state (resting) conditions
    o in our model cell
      \( E_m -71 \) mV
      \( E_k -81 \) mV
      \( E_{Na} +58 \) mV
      thus, \( E_m \) is much closer to \( E_k \) than to \( E_{Na} \)
    o \( E_k \) appear to be have more influence on the resting potential
    o why?
      because resting membrane is more permeable to \( K^+ \) than to 
      \( Na^+ \)
    o why?
      because of the state of the ion channels through which these 
      two ions flow
      under resting conditions, \( K^+ \) crosses the membrane much more 
      readily than \( Na^+ \)
      If both ions have the same charge, how could a channel let 
      one ion (e.g., \( K^+ \)) pass fairly readily while excluding the other 
      (e.g., \( Na^+ \))?
      because the two ions have a different *charge density* and 
      *radius of hydration*
      \( K^+ \) is larger than \( Na^+ \) but has the same charge. Thus the 
      charge *density* at the surface of the \( K^+ \) ion is lower than the 
      density at the surface of the \( Na^+ \) ion, and a smaller cloud of 
      water molecules surrounds \( K^+ \) than \( Na^+ \).

  • These characteristics can influence the interaction between ions and 
    channels.
  • the resting membrane potential depends both on \( K^+ \) and \( Na^+ \), but it is 
    more strongly influenced by \( K^+ \) than by \( Na^+ \)
resting membrane potential reflects a compromise: it lies between the equilibrium potentials for $K^+$ and $Na^+$, but much closer to $E_k$.

- How can we calculate the value of $E_m$?
  - If only $K^+$ could cross membrane, then the Nernst equation for $K^+$ would do the trick.
  - Given that both $K^+$ and $Na^+$ can cross, we must modify the Nernst equation to reflect this fact.

- **Hodgkin-Katz-Goldman equation**
  - General form (Hodgkin-Katz-Goldman Equation)
    - Under resting conditions, $Cl^-$ has very little influence on the membrane potential.
    - Thus, we can simplify the equation to account only for $K^+$ and $Na^+$.
  - Note that if the sodium permeability is set to zero, this simplified expression reduces to the Nernst equation for potassium.
  - The Hodgkin-Katz-Goldman equation can be seen as a generalization of the Nernst equation.
    - The concentrations of more than one permeant ion are taken into account.
    - The influence of each permeant ion on the membrane potential is specified by weighting the concentration of that ion by its membrane permeability.

- **Permeability vs conductance**
  - The Hodgkin-Katz-Goldman equation is very useful for calculating membrane potentials and their dependence on concentration gradients.
    - However, it doesn't directly predict the fluxes of ions.
    - We need to know about fluxes if we are to understand the job of the membrane pumps.
    - To work with fluxes, we need to introduce a new term, conductance.
    - Also, conductances are much more easily measured than permeabilities.
  - **Permeability** describes the ease with which an ion can move through the membrane.
  - **Conductance** describes the ability of a given ion species to carry electrical current across the membrane.
    - Conductance depends on permeability, but it also depends on concentration.
      - Permeability of the membrane could be high (channels could be open), but if few ions of this type are present, then that ion species can't carry much current.
    - [It may help here to review some basic definitions of electrical terms.]

• **Parallel conductance model**
  - now that we know about conductance, we can make use of a very important relationship, **Ohm’s law**, that allows us to predict the magnitude of ion fluxes
    - Ohm’s law specifies the relationship between current (flux of charge carriers), electromotive force (the force that drives the fluxes), and conductance
      - current (I) equals the product of conductance (g) and driving force (E)
        - \( I = g \times E \)
        - this is Ohm’s law expressed in terms of transmembrane ionic currents
          - (g is the inverse of resistance (i.e., \( g = 1/R \)))
  
• **concept of driving force**
  - when \( E_m = E_{ion} \) there is no electromotive force operating on that ion because the ion in question is at equilibrium
  - the strength of the electromotive force depends on the difference between the membrane potential and the equilibrium potential for an ion (e.g. \( E_m - E_k \))
  - at rest, \( I_m = 0 \) (if there were a net flow of current across the membrane, the membrane potential would not be at rest, it would be changing)
  - therefore, at rest, \( I_k = -I_{Na} \) (in a cell that pumps these ions across the membrane in a 1:1 ratio)
  - from this assumption, we can demonstrate that \( E_m \) depends on the ratio of sodium to potassium conductance, \( g_{Na}/g_{k} \) (**Parallel-Conductance Equation**)
    - if \( g_{Na} \) is much greater than \( g_{k} \), then the membrane potential will approach the sodium equilibrium potential
    - if \( g_{Na} \) is much less than \( g_{k} \), then the membrane potential will approach the potassium equilibrium potential
    - at rest, \( g_{Na} \) is considerably less than \( g_{k} \), and thus, the membrane potential is close to the potassium equilibrium potential
      - however, because \( g_{Na} \neq 0 \) under resting conditions, the membrane potential is "pulled" slightly away from \( E_k \), in the direction of the sodium equilibrium potential
  
• this model is very useful, because it allows us to predict both the changes in membrane potential and the ion fluxes that result from changes in conductances
  - conductances change as a result of the opening and closing of ion channels
  - as we will see, this is basis for post-synaptic potentials and action potentials
Interim summary: K⁺ and Na⁺ in the resting state

- a relatively small force drives K⁺ through a relatively substantial conductance
- a relatively large force drives Na⁺ though a much smaller conductance
  - why is the force on K⁺ small?
    - because the membrane potential is almost negative enough to balance the concentration gradient for K⁺
  - why is the resting K⁺ conductance appreciable?
    - because some K⁺ channels are open at rest
  - why is the force on Na⁺ large?
    - because both the concentration gradient and the electrostatic gradients for Na⁺ point in the same direction
  - why is the resting Na⁺ conductance small?
    - because most Na⁺ channels are closed at rest
- the driving force for Na⁺ is larger than the driving force on K⁺, but the conductance to Na⁺ is smaller than the conductance to K⁺
  - given that current is equal to the product of driving force and conductance, the transmembrane currents carried by K⁺ and Na⁺ are pretty similar under resting conditions
    - in a simplified model cell, we can treat the two currents as equal and opposite
      - the first three equations under the heading "Parallel-Conductance Equation" are based on this assumption
      - to make the model cell more realistic, we take into account the fact that the Na⁺ current is about 1.5 times larger than the K⁺ current
        - the final equation under the heading "Parallel-Conductance Equation" incorporates a term for the Na⁺/K⁺ transport ratio
  - the constant leak of Na⁺ and K⁺ across the membrane would eventually change the membrane potential if the cell did not use energy to oppose them
    - the cell does expend energy for this purpose, pumping ions across the membrane at rates that are equal and opposite to the passive fluxes
    - the pump simply offsets the currents flowing passively across the membrane, thereby holding the ion concentrations constant
      - thus, in the final equation under the heading "Parallel-Conductance Equation," setting the term for the Na⁺/K⁺ transport ratio to 1.5, will also set the ratio of I₉Na/I₉K to 1.5
- Because the Na⁺/K⁺ pump offsets the leakage of Na⁺ and K⁺ across the membrane, the cell remains in a steady state
unless subject to outside influences, this model cell will have an unchanging resting potential, and unchanging concentrations of sodium and potassium
  - it must expend energy to achieve this steady state

Role of the Na\(^+\)/K\(^+\) pump

- as mentioned above, the pump is responsible for the maintenance of concentration gradients
- in simplified model cell, the pump must compensate for equal and opposite fluxes of K\(^-\) and Na\(^+\)
- in the more realistic model, there is roughly a 3:2 exchange of Na\(^+\) and K\(^-\)
  - thus, pump is electrogenic, doing both chemical and electrical work
    - in a cell with an electrogenic pump, speeding up or slowing the pump will change the membrane potential
- as an exercise, try incorporating the 3:2 exchange of Na\(^+\) and K\(^-\) while solving the
  - Hodgkin-Katz-Goldman equation
  - parallel-conductance equation
- pump is an ATPase, and enzyme that breaks down ATP to AMP, thus harnessing energy
  - this energy is used to pump ions against concentration gradient and, in the cases where the pump is electrogenic, to do electrostatic work
- the Na\(^+\)/K\(^+\) pump is one of many membrane pumps
  - some cells also have Cl\(^-\) pumps
  - all have Ca\(^{++}\) pumps

Unfinished business: what about Cl\(^-\)?

- in neurons without a Cl\(^-\) pump, the concentrations of Cl\(^-\) adjusts so that the equilibrium potential for this ion equals the resting membrane potential
- in neurons with a Cl\(^-\) pump, the equilibrium potential for Cl\(^-\) differs from the resting potential by a few millivolts
  - resting Cl\(^-\) conductance is so low, that this ion has little influence on the resting potential
Summary of the resting state

- an uneasy balance of forces and fluxes
- Na\(^+\) and K\(^+\) leak across the membrane
- the Na\(^+\)/K\(^+\) pump compensates for these fluxes
- thus, ion concentrations are held constant
- given that the resting value of \(g_{Na}\) is considerably less than the resting value of \(g_k\), the membrane potential is close to the potassium equilibrium potential, \((E_m\) is about -60 to -90 millivolts (negative inside))
- changing \(g_{Na}/g_k\) (or certain other conductances) will upset this uneasy balance of forces and fluxes
  - such changes are the basis of the action potentials and post-synaptic potentials we will study in the coming lectures