Human Physiology I

Second Year Pharmacy Students

Chapter 3: Membrane Potential

Part 1

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First Semester 2020/2021

Membrane Potential

■ The term **membrane potential** refers to a separation of opposite charges across the membrane ,or, to a difference in the relative number of cations and anions in the ICF and ECF.

■ Opposite charges tend to attract each other and like charges tend to repel each other.

■ Work must be performed (energy expended) to separate opposite charges after they have come together.

Membrane Potential

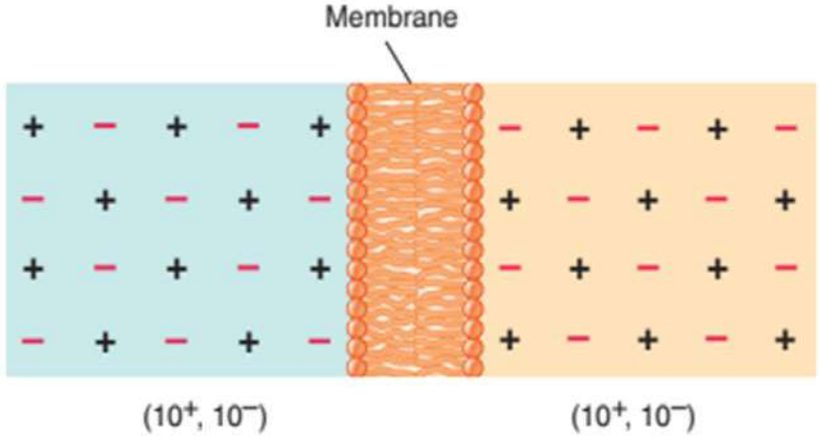
- Conversely, when oppositely charged particles have been separated, the electrical force of attraction between them can be harnessed to perform work when the charges are permitted to come together again.
- A separation of charges across the membrane is called a **membrane potential** because separated charges have the potential to do work. Membrane Potential is measured in Millivolt (mV) because the membrane potential is relatively low.

Membrane Potential

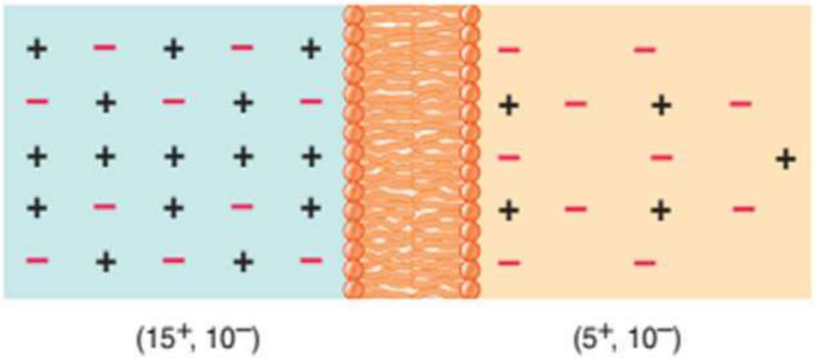
- The concept of potential is fundamental to understanding much of physiology of nerve and muscle, thus, it is important to understand what this term means.

Membrane Potential

- The membrane in **Figure (a)** is **electrically neutral**: with an equal number of positive (+) and negative charges (-) on each side of the membrane, no membrane potential exists. (When the positive and negative charges are equally balanced on each side of the membrane, no membrane



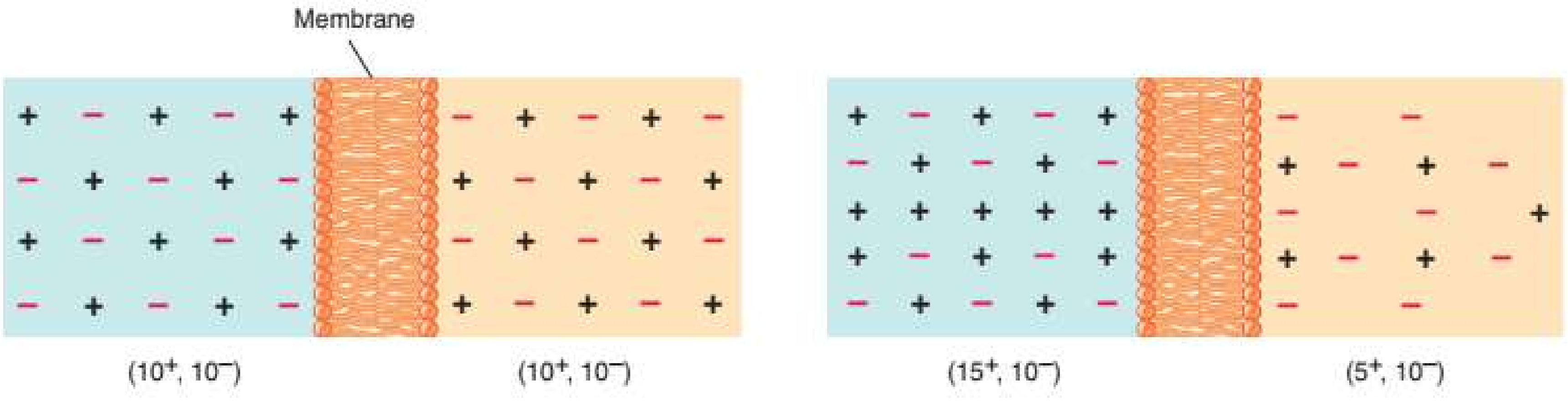
(a) Membrane has no potential



(b) Membrane has potential

Membrane Potential

In **Figure (b)**, some of the positive charges from the right side have been moved to the left. Now the left side has an excess of positive charges, leaving an excess of negative charges on the right. (When opposite charges are separated across the membrane, membrane potential exists).



(a) Membrane has no potential

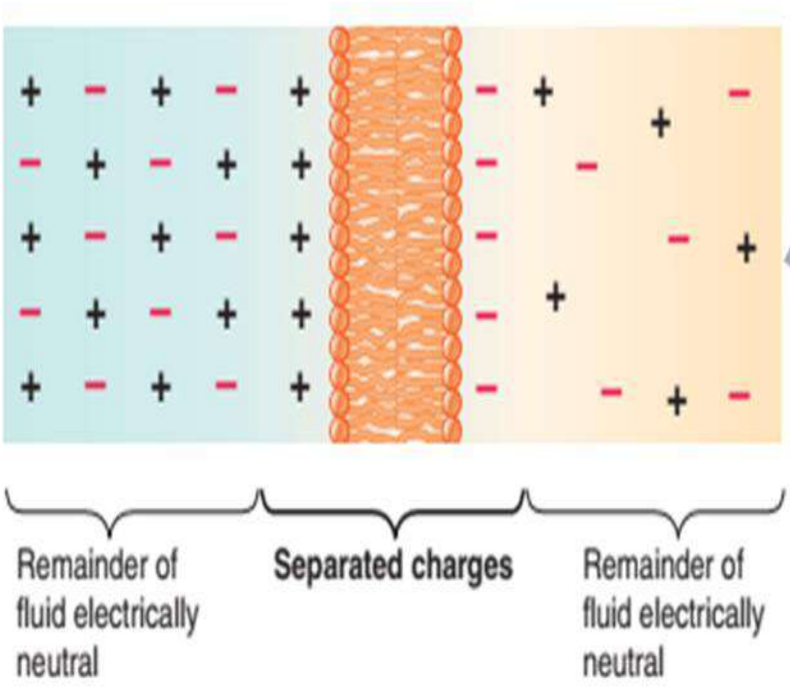
(b) Membrane has potential

Membrane Potential

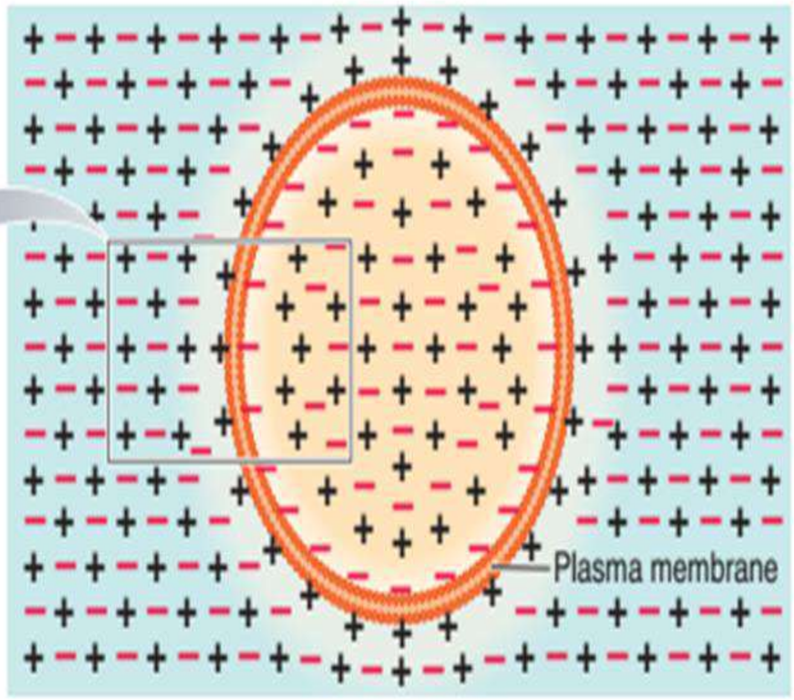
■ In other words, there is a separation of opposite charges across the membrane, or a difference in the relative number of positive and negative charges between the two sides. That is, now **a membrane potential** exists.

Membrane Potential

- The **attractive force** between the separated charges causes them to accumulate in **a thin layer** along the outer and inner surfaces of the plasma membrane **(Figure (c).**



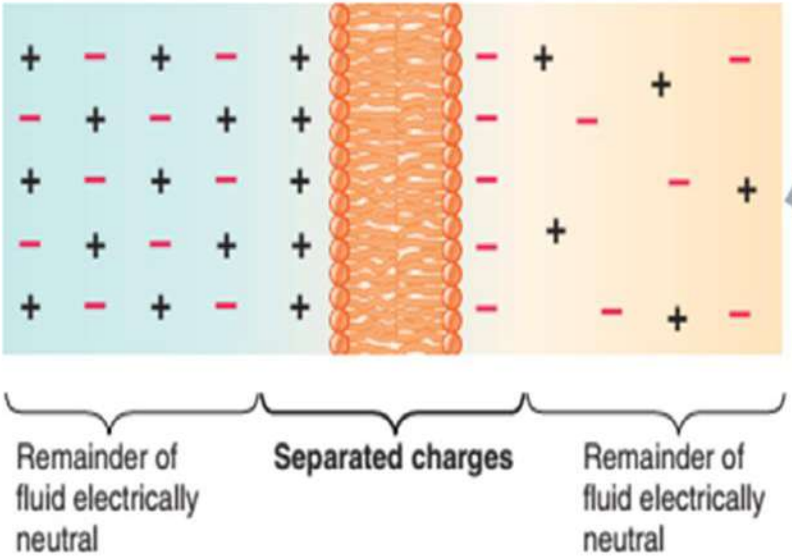
(c) Separated charges responsible for potential



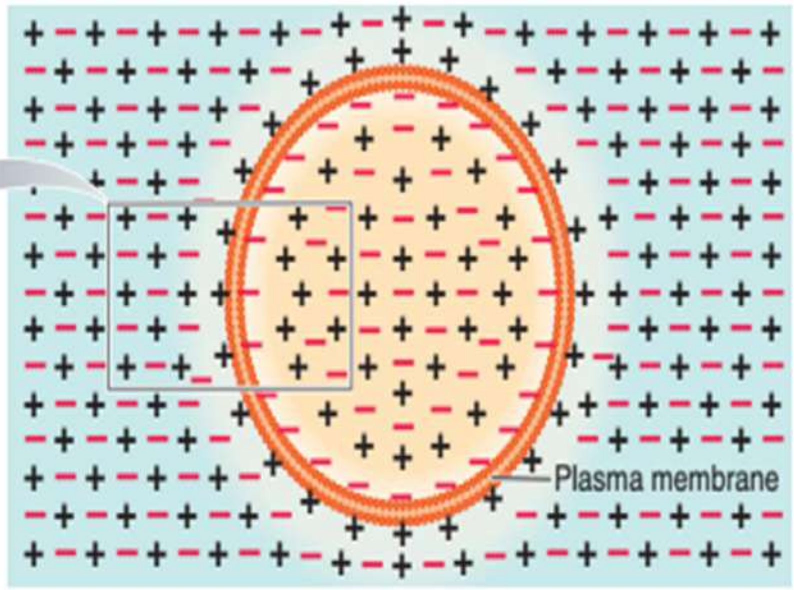
(d) Separated charges forming a layer along plasma membrane

Membrane Potential

- These **separated charges** represent only **a small fraction** of the total number of charged particles (ions) present in the ICF and ECF, and the vast majority of the fluid inside and outside the cells is electrically neutral **(Figure (d).**



(c) Separated charges responsible for potential



(d) Separated charges forming a layer along plasma membrane

Membrane Potential

■ The **electrically balanced ions** can be ignored, because they **do not** contribute to membrane potential. Thus, an almost **insignificant** (very small) fraction of the total number of charged particles present in the body fluids is responsible for the **membrane potential.**

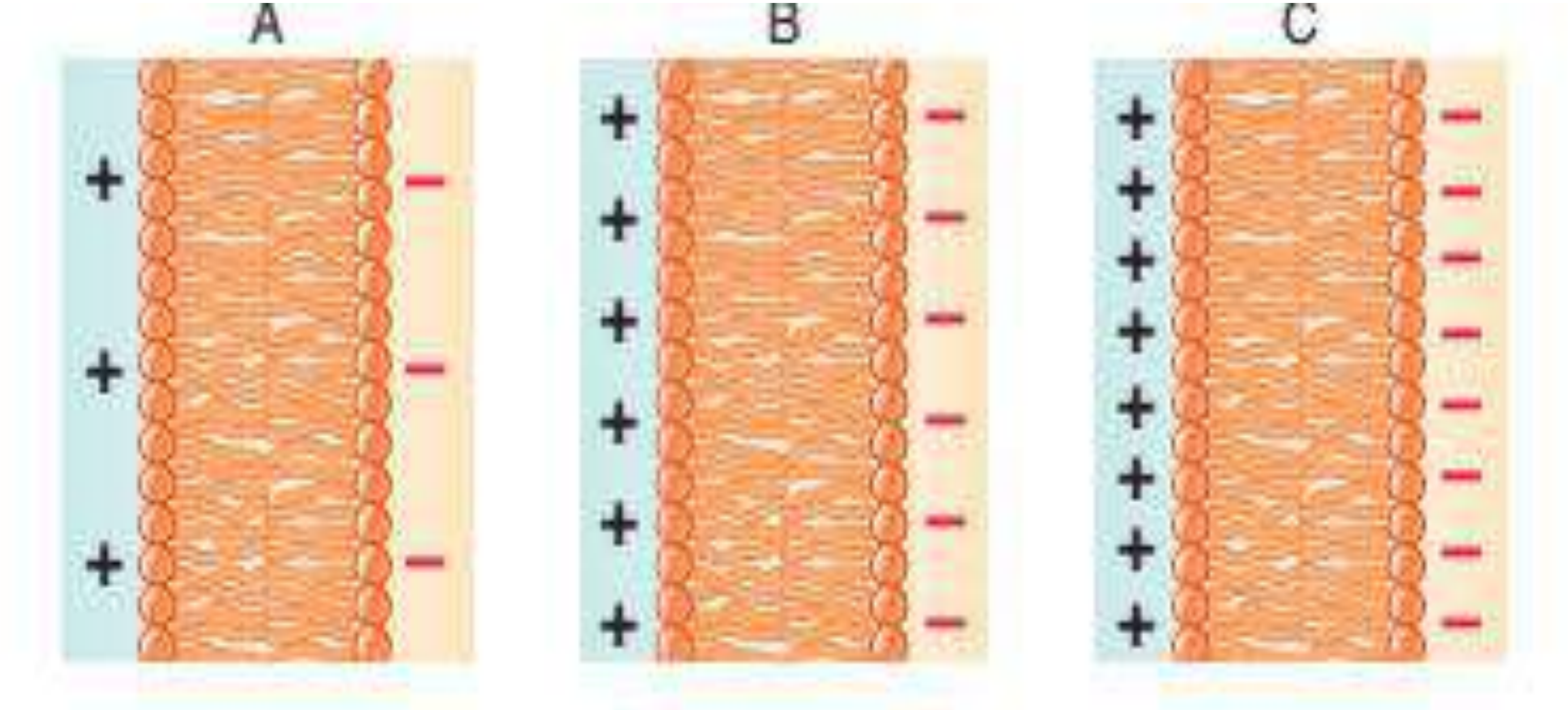
Membrane Potential

■ Note that **the membrane itself** is **not charged**. The term **membrane potential** refers to the **difference** in **charge** between the **wafer-thin regions** of **ICF** and **ECF** lying next to the **inside** and **outside** of the membrane, respectively.

■ The **magnitude** of the **potential** depends on the **number** of opposite charges separated: The **greater** the **number** of **charges** separated, the **larger** the **potential.**

Membrane Potential

Therefore, in **Figure (e)** membrane B has more potential than A and less potential than C.



(e) Magnitude of potential: membrane B has more potential than membrane A and less potential than membrane C

Membrane Potential

- **Membrane potential** is due to **differences in the concentration** and **permeability** of **key ions:**
- All cells have membrane potential. The cells of excitable tissues (**nerve cells** and **muscle cells)** which have the ability to produce **rapid, transient changes** in their **membrane potential** when **excited**. These **brief fluctuations** in **potential** serve as **electrical signals.**

Membrane Potential

■ The **constant membrane potential** present in the cells of both **non-excitable** and **excitable tissues** when they are at **rest**, that is, when they are **not producing electrical signals**, is known as the **resting membrane potential (R M P).**

■ **Generation and maintenance of R M P:**

■ The **unequal** distribution of **a few** key ions between the ICF and ECF and their **selective movement** through the plasma membrane are **responsible** for the **electrical properties** of the membrane.

Membrane Potential

■ In the body, **electrical charges** are carried by **ions.**

■ The **ions primarily responsible** for the **generation** of the RMP are Na^+, K^+, and A^- ((the large, negatively charged (anionic) intracellular proteins).

■ **Other ions** (calcium, magnesium, chloride, bicarbonate, and phosphate, to name a few) **do not** contribute **directly** to the **resting electrical properties** of plasma membrane in **most** cells, even though they **play other important roles** in the body.

Membrane Potential

- The **concentrations** and **relative permeabilities** of **the ions critical** to **membrane electrical activity** are compared in the following table:

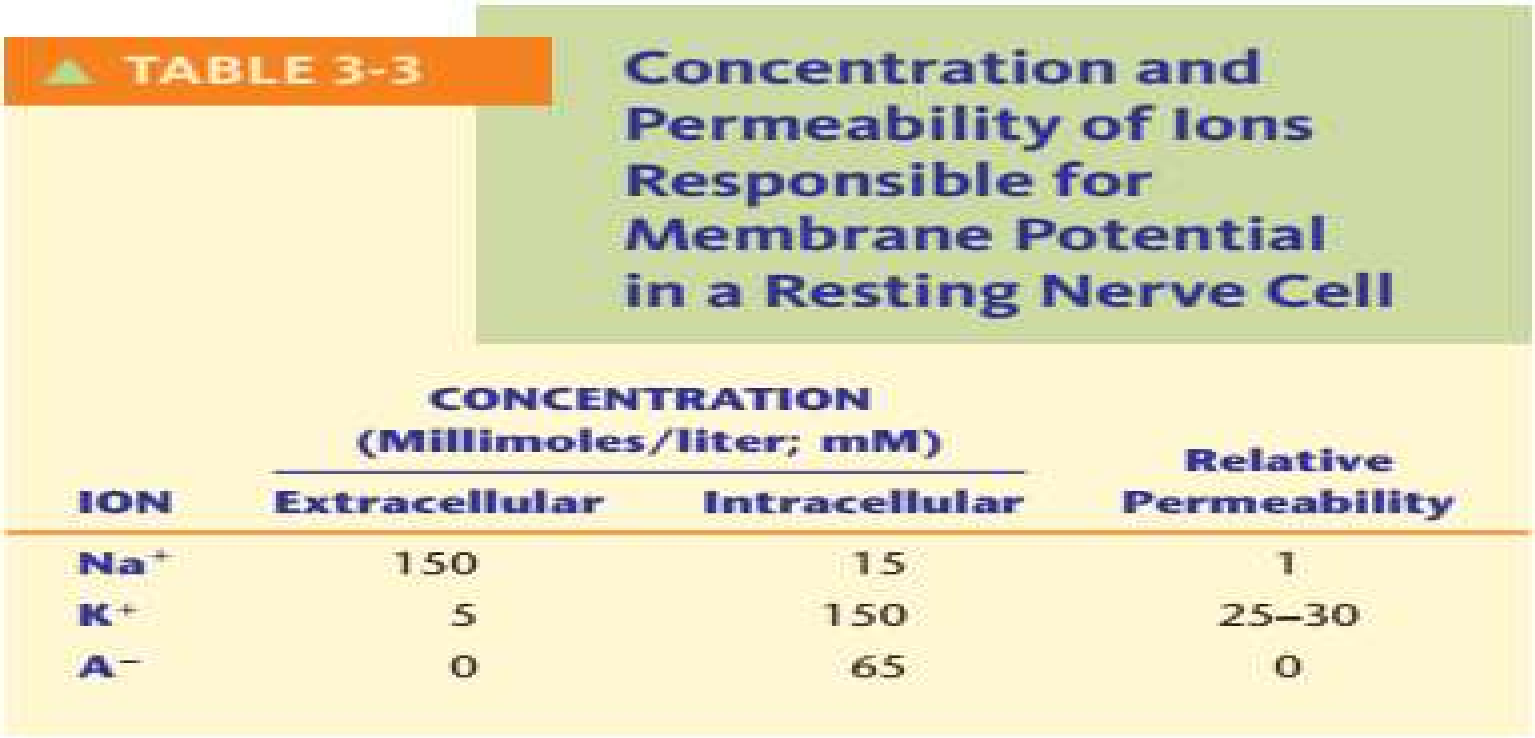


TABLE 3-3

Concentration and Permeability of Ions Responsible for Membrane Potential in a Resting Nerve Cell

ION	CONCENTRATION (Millimoles/liter; mM) Extracellular	CONCENTRATION (Millimoles/liter; mM) Intracellular	Relative Permeability
Na^+	150	15	1
K^+	5	150	25–30
A^-	0	65	0

Membrane Potential

■ Note that **Na^+** is **more concentrated** in the **ECF** and **K^+** is **more concentrated** in the **ICF**. These **concentration differences** are **maintained** by the **Na^+–K^+ pump** at the **expense** of **energy.**

■ Because the plasma membrane is **virtually impermeable** to **A^-,** these **large, negatively charged proteins** are found **only inside** the **cell**. After they have been **synthesized** from **amino acids** transported **into** the cell, they remain **trapped** within the cell.

Membrane Potential

■ In addition to **the active carrier mechanism**, **Na$^+$** and **K$^+$** can **passively** cross the membrane through **protein channels specific** for them. It is usually **much easier** for **K$^+$ than** for **Na$^+$** to **get through (cross)** the membrane because the membrane **typically** has **many more channels open** for **passive K$^+$ traffic than** for **passive Na$^+$ traffic**. At **resting potential** in a **nerve cell**, the membrane is **typically** about **25-30 times more permeable** to **K$^+$ than** to **Na$^+$.**

Membrane Potential

■ **Analysis** of the **forces** acting **across** the plasma membrane:

1. The **direct contributions** of the **Na^+-K^+ pump** to **membrane potential.**

2. The **effect** that the **movement** of **K^+ alone** would have on **membrane potential.**

3. The **effect** that the **movement** of **Na^+ alone** would have on **membrane potential.**

4. The **effect** when the **movement** of **both K^+** and **Na^+** would have on **membrane potential.**

Membrane Potential

- **Remember** that:

1. The **concentration gradient** for K^+ will always be outward and the concentration gradient for Na+ will always be inward (because the Na^+-K^+ pump maintains a higher concentration of K^+ inside the cell and a higher concentration of Na^+ outside the cell).

2. Because K^+ and Na^+ are both cations (positively charged), the **electrical gradient** for both will always be **toward** the **negatively charged side** of the membrane.

Membrane Potential

1. Effect of the Na^+–K^+ pump on membrane potential:

■ The Na^+–K^+ pump transports 3 Na^+ out for every 2 K^+ it transports in. Because Na^+ and K^+ are positive ions, this unequal transport separates charges across the membrane, with the outside becoming more positive and the inside becoming more negative as more positive ions are transported out than in. However, this mechanism only separates enough charges to generate an almost negligible membrane potential of 1-3 mV, with the interior **negative** to the exterior of the cell.

Membrane Potential

■ The vast majority of the membrane potential results from the passive diffusion of K^+ and Na^+ **down concentration gradients**.

■ Thus, the main role of the Na^+-K^+ pump in producing membrane potential is **indirect**, through its critical contribution to maintaining the concentration gradients directly responsible for the ion movements that generate most of the potential.

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Chapter 3: Membrane Potential
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2. Effect of the movement of K^+ alone on the membrane potential: Equilibrium potential for K^+:

■ Let’s consider **a hypothetical situation** characterized by:

1. The concentrations that exist for K^+ and A^- across the plasma membrane.

2. Free permeability of the membrane to K^+ but **not** to A^-

3. No potential yet present.

Membrane Potential

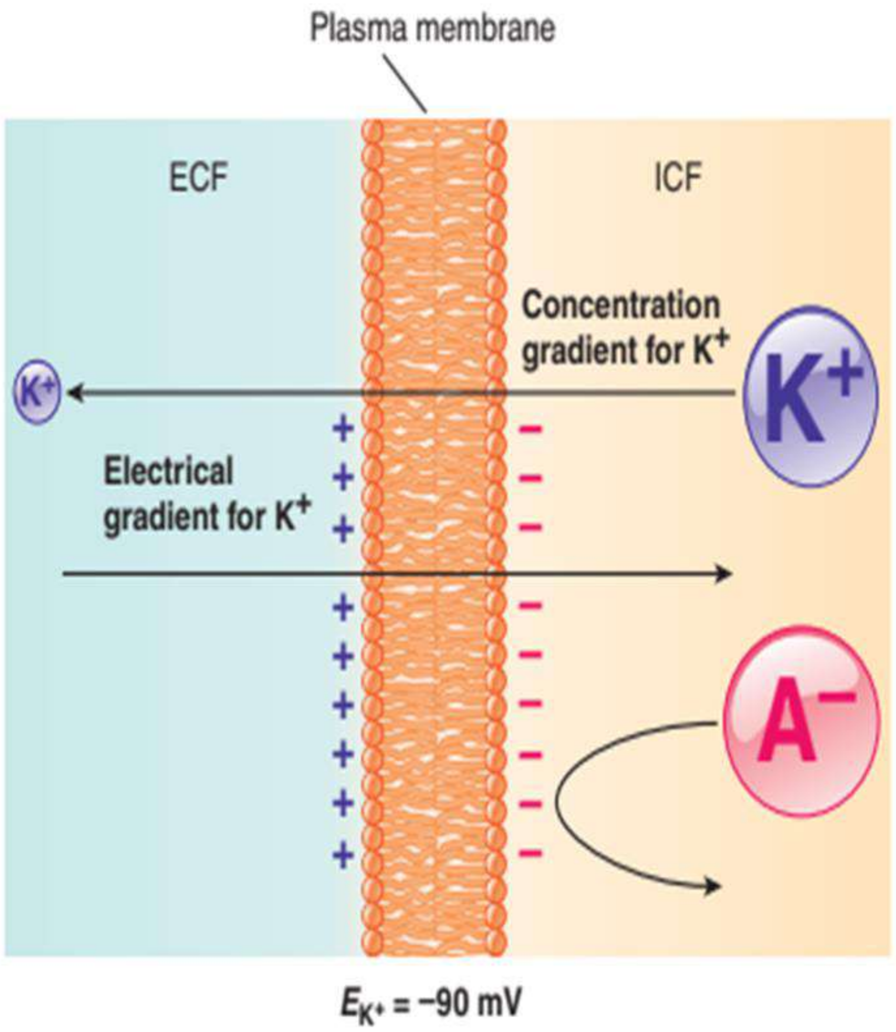
■ The **concentration** gradient for K^+ would tend to move K^+ **out** of the cell. Because the membrane is **permeable** to K^+, these ions would readily pass through, carrying their positive charge with them, so **more positive charges** would be on the **outside.**

■ At the same time, **negative** charges in the form of **A^-** would be left behind on **the inside** because the large protein anions cannot diffuse out, despite a tremendous **concentration gradient**.

Membrane Potential

- **A membrane potential** would now **exist**.
- Because **an electrical** gradient would also be **present**, K^+ would be **attracted toward the negatively charged interior** and **repelled** by **the positively charged exterior.**
- Thus, **2 opposing forces** would **now** be **acting** on **K^+**: the **concentration** gradient tending to **move K^+ out** of the cell and the **electrical** gradient tending to **move K^+ into** the cell.

Membrane Potential



1 The concentration gradient for K^+ tends to move this ion out of the cell.

2 The outside of the cell becomes more positive as K^+ ions move to the outside down their concentration gradient.

3 The membrane is impermeable to the large intracellular protein anion (A^-). The inside of the cell becomes more negative as K^+ ions move out, leaving behind A^-.

4 The resulting electrical gradient tends to move K^+ into the cell.

5 No further net movement of K^+ occurs when the inward electrical gradient exactly counterbalances the outward concentration gradient. The membrane potential at this equilibrium point is the equilibrium potential for K^+ (E_{K^+}) at −90 mV.

● **FIGURE 3-21** **Equilibrium potential for K^+.**

Membrane Potential

- **Initially**, the **concentration** gradient would be **stronger** than the **electrical** gradient, so **net movement** of K^+ **out** of the cell would **continue**, and the **membrane potential** would **increase.** As **more** and **more K^+** moved **out** of the cell, however, **the opposing electrical gradient** would also become **stronger** as the **outside** became **increasingly more positive** and the **inside more negative**. One might think that the **outward concentration gradient** for K^+ would **gradually decrease** as K^+ **leaves** the cell **down** this **gradient**.

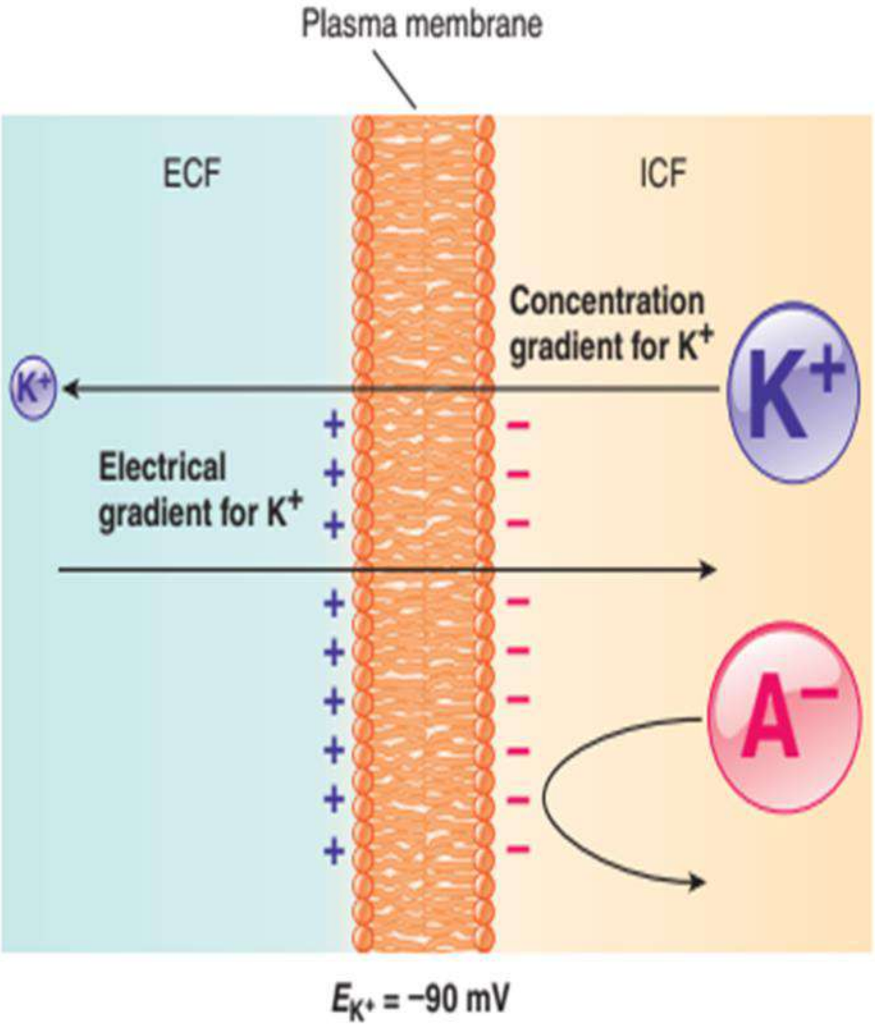
Membrane Potential

- **Surprisingly**, however, the **K$^+$ concentration** gradient would remain **essentially constant** despite **the outward movement** of K$^+$. The **reason** is that even **infinitesimal movement** of K$^+$ **out** of the cell would bring about **large changes** in **membrane potential**. Accordingly, such **an extremely small number** of K$^+$ ions would have to leave the cell to establish an **opposing electrical gradient** that the **K$^+$ concentration inside** and **outside** the cell would remain **essentially unaltered**.

Membrane Potential

- As K^+ continued to move out down its unchanging concentration gradient, the inward electrical gradient would continue to increase in strength. Net outward movement would gradually be reduced as the strength of the electrical gradient **approached** that of the concentration gradient. Finally, when these 2 forces exactly balanced each other (when they were in equilibrium), **no** further net movement of K^+ would occur. The **potential** that would exist at this equilibrium is known as the **equilibrium potential** for K^+ (E_{K+}).

Membrane Potential



1 The concentration gradient for K^+ tends to move this ion out of the cell.

2 The outside of the cell becomes more positive as K^+ ions move to the outside down their concentration gradient.

3 The membrane is impermeable to the large intracellular protein anion (A^-). The inside of the cell becomes more negative as K^+ ions move out, leaving behind A^-.

4 The resulting electrical gradient tends to move K^+ into the cell.

5 No further net movement of K^+ occurs when the inward electrical gradient exactly counterbalances the outward concentration gradient. The membrane potential at this equilibrium point is the equilibrium potential for K^+ (E_{K^+}) at −90 mV.

● **FIGURE 3-21 Equilibrium potential for K^+.**

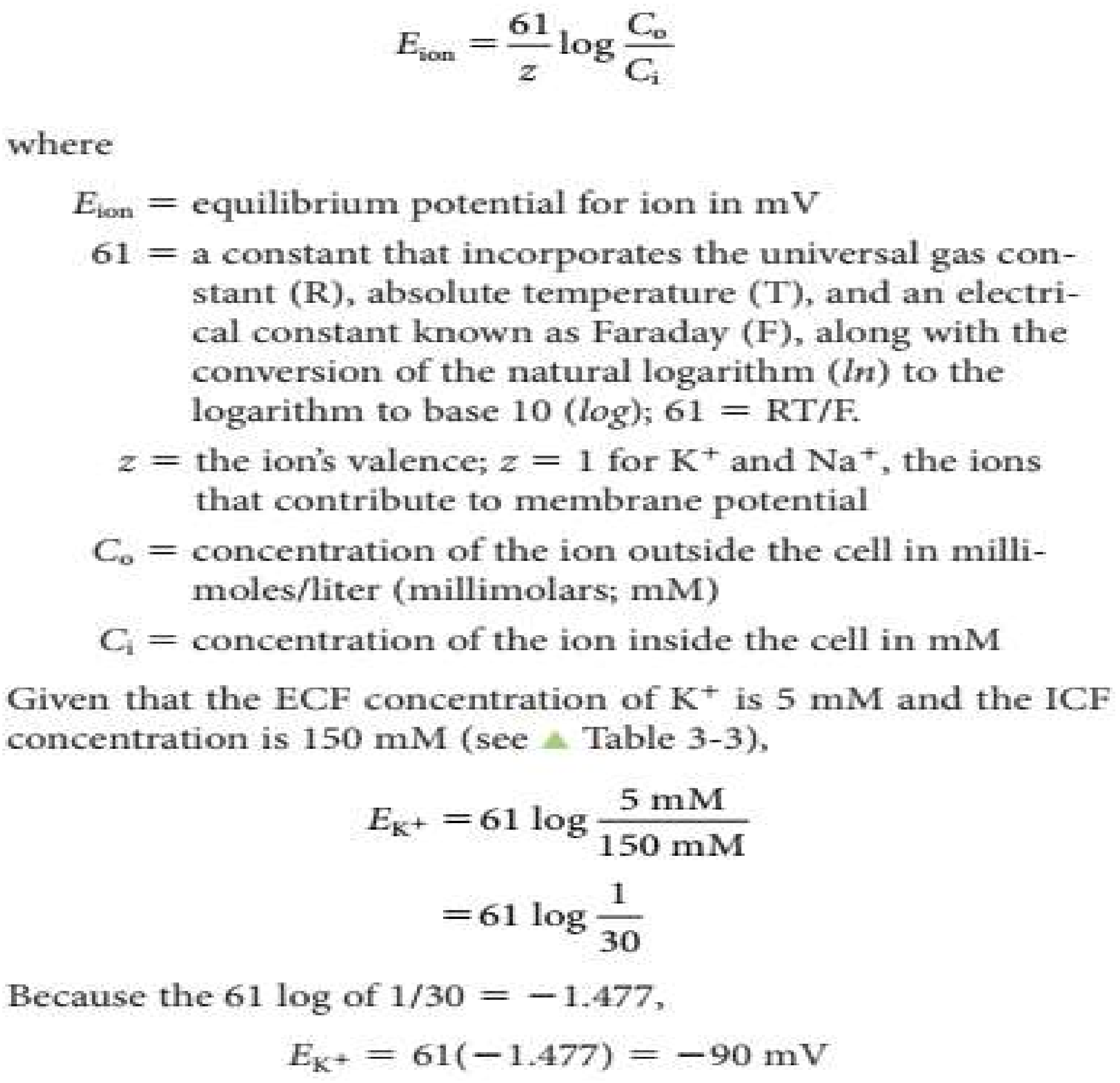
Membrane Potential

- At this point, a large concentration gradient for K^+ would still exist, but no more net movement of K^+ out of the cell would occur down this concentration gradient because of the exactly equal opposing electrical gradient.
- The membrane potential at E_{K+} is -90 mV. The sign always designates the polarity of the excess charge on the inside of the membrane. A membrane potential of -90 mV means that the potential is of a magnitude of 90 mV, with the inside being negative relative to the outside.

Membrane Potential

- A potential of +90 mV would have the same strength, but the inside would be more positive than the outside.
- The equilibrium potential for a given ion with differing concentrations across a membrane can be calculated by means of the Nernst equation as follows:

Membrane Potential



$$E_{\text{ion}} = \frac{61}{z} \log \frac{C_o}{C_i}$$

where

E_{ion} = equilibrium potential for ion in mV

61 = a constant that incorporates the universal gas constant (R), absolute temperature (T), and an electrical constant known as Faraday (F), along with the conversion of the natural logarithm (*ln*) to the logarithm to base 10 (*log*); 61 = RT/F.

z = the ion's valence; $z = 1$ for K^+ and Na^+, the ions that contribute to membrane potential

C_o = concentration of the ion outside the cell in millimoles/liter (millimolars; mM)

C_i = concentration of the ion inside the cell in mM

Given that the ECF concentration of K^+ is 5 mM and the ICF concentration is 150 mM (see ▲ Table 3-3),

$$E_{K^+} = 61 \log \frac{5\text{ mM}}{150\text{ mM}}$$

$$= 61 \log \frac{1}{30}$$

Because the 61 log of 1/30 = −1.477,

$$E_{K^+} = 61(-1.477) = -90\text{ mV}$$

Membrane Potential

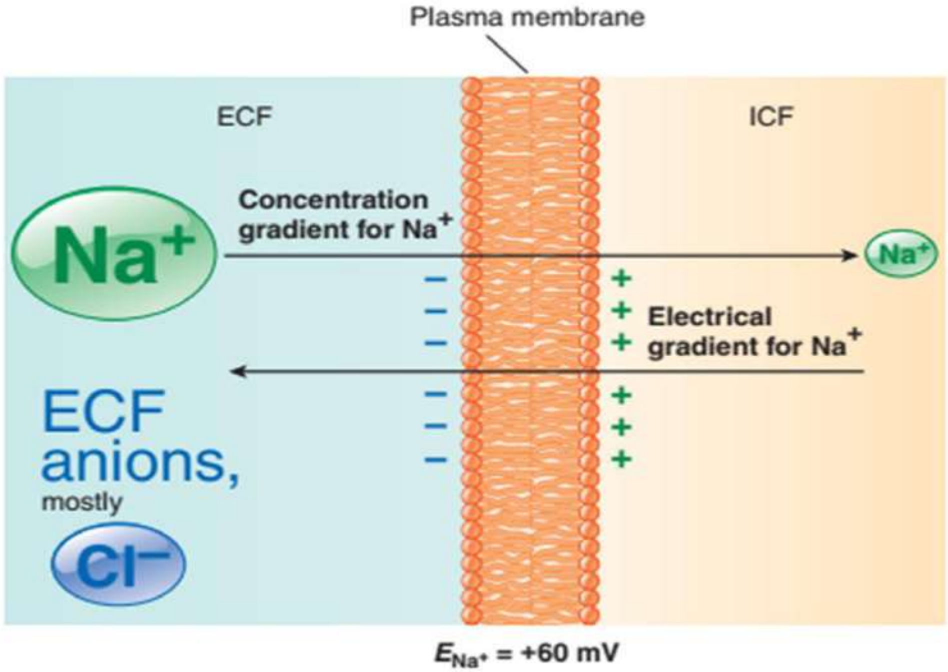
■ Because 61 is a constant, the equilibrium potential is essentially a measure of the membrane potential, that is, the magnitude of the electrical gradient that exactly counterbalances the concentration gradient for the ion (that is, the ratio between the ion’s concentration outside and inside the cell). The larger the concentration gradient is for an ion, the greater the ion’s equilibrium potential. A comparably greater opposing electrical gradient would be required to counterbalance the larger concentration gradient.

3. Effect of movement of Na^+ alone on membrane potential: Equilibrium Potential for Na^+:

■ A similar hypothetical situation could be developed for Na^+ **alone**. The **concentration** gradient for Na^+ would move this ion into the cell, producing a buildup of positive charges on the interior of the membrane and leaving negative charges unbalanced outside (primarily in the form of chloride, Cl^-) (Note that: Na^+ and Cl^- , that is, salt, are the predominant ECF ions).

Membrane Potential

- Net inward movement would continue until equilibrium is established by the development of an opposing **electrical** gradient that exactly counterbalance the concentration

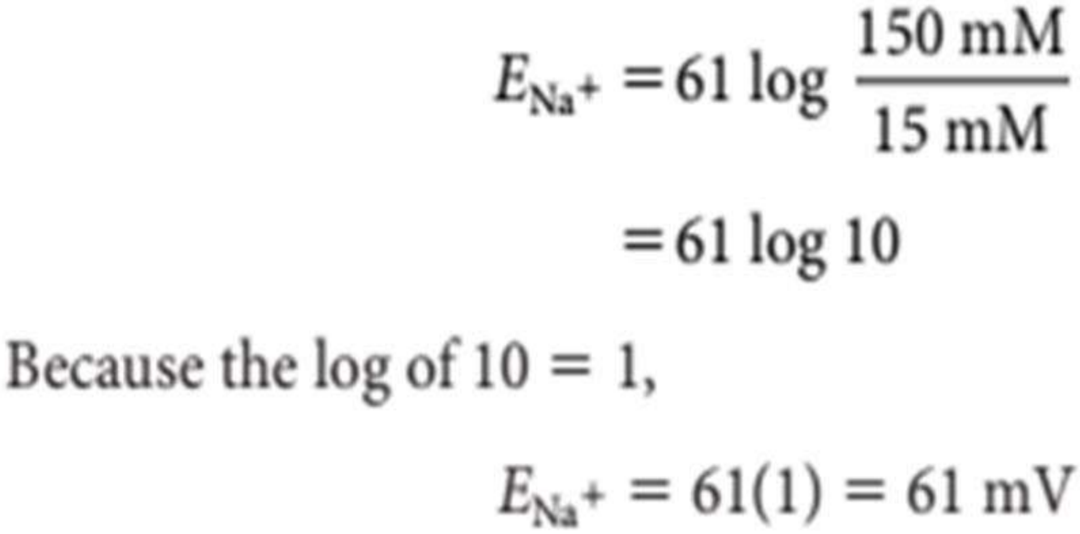


1. The concentration gradient for Na^+ tends to move this ion into the cell.
2. The inside of the cell becomes more positive as Na^+ ions move to the inside down their concentration gradient.
3. The outside becomes more negative as Na^+ ions move in, leaving behind in the ECF unbalanced negatively charged ions, mostly Cl^-.
4. The resulting electrical gradient tends to move Na^+ out of the cell.
5. No further net movement of Na^+ occurs when the outward electrical gradient exactly counterbalances the inward concentration gradient. The membrane potential at this equilibrium point is the equilibrium potential for Na^+ (E_{Na^+}) at +60 mV.

● **FIGURE 3-22 Equilibrium potential for Na^+.**

Membrane Potential

- At this point, given the concentrations for Na^+, the equilibrium potential for Na^+ (E_{Na+}) as calculated by the Nernst equation would be 61 mV



$$E_{Na^+} = 61 \log \frac{150 \text{ mM}}{15 \text{ mM}}$$

$$= 61 \log 10$$

Because the log of 10 = 1,

$$E_{Na^+} = 61(1) = 61 \text{ mV}$$

Membrane Potential

- In this case, the **inside** of the cell would be **positive**, in contrast to the **equilibrium potential** for **K^+.** The **magnitude** of E_{Na+} is somewhat **less** than for E_{K+} (61 mV compared to 90 mV) because the **concentration gradient** for **Na^+** is **not** as **large**; thus, the **opposing electrical gradient** is **not** as **great** at **equilibrium.**

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Membrane Potential

4. Concurrent K$^+$ and Na$^+$ effects on membrane potential:

■ **Neither** K$^+$ **nor** Na$^+$ exists **alone** in the **body fluids**, so equilibrium potentials are **not** present in body cells. They exist **only** in hypothetical or experimental conditions. In a living cell, the effects of **both** K$^+$ and Na$^+$ must be taken into account.

■ The **greater** the **permeability** of the plasma membrane for a **given ion**, the **greater** the **tendency** is the for that ion to **drive** the **membrane potential toward** the **ion's own equilibrium potential.**

Membrane Potential

- Because the membrane at **rest** is 25-30 times more permeable to K^+ than to Na^+, K^+ passes more readily than Na^+; thus, K^+ **influences** the **RMP** to **a much greater extent than** Na^+. K^+ acting **alone** would **establish** an **equilibrium potential** of -90 mV. The membrane is **somewhat** permeable to Na^+, so some Na^+ enters the cell in a **limited attempt** to reach its equilibrium potential. This Na^+ entry neutralizes, or cancels, some of the potential that would have been produced by K^+ alone if Na^+ were not present

Membrane Potential

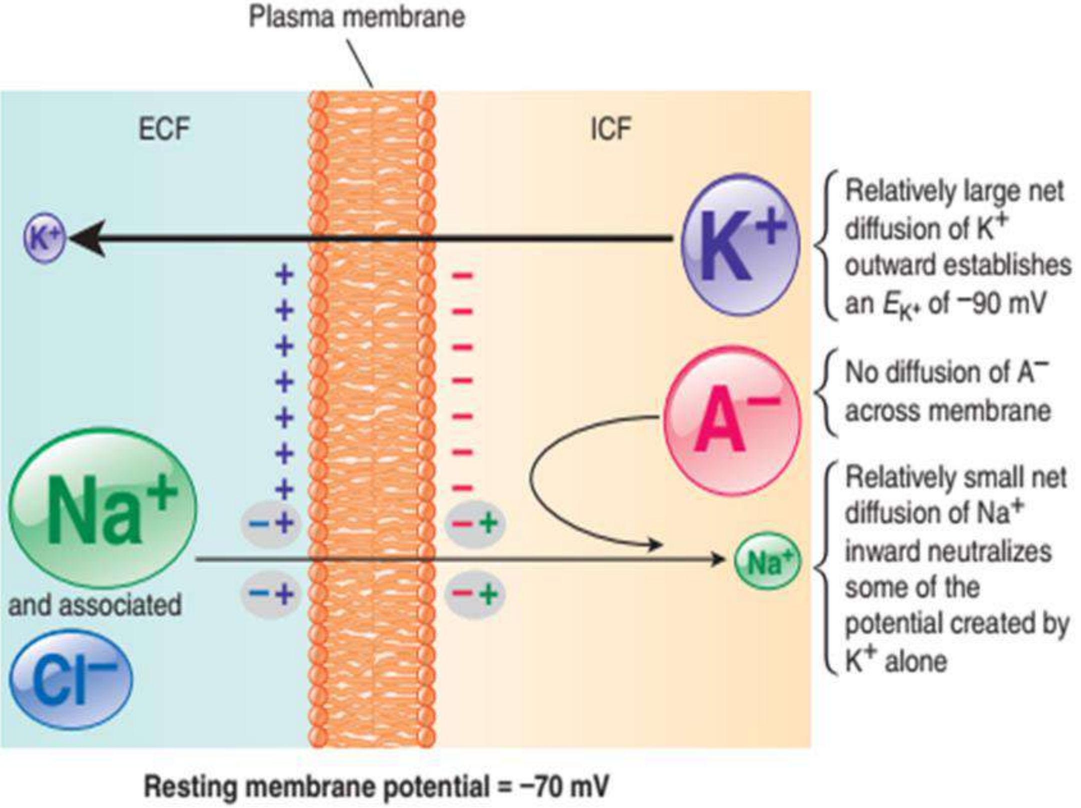
1 The Na^+–K^+ pump actively transports Na^+ out of and K^+ into the cell, keeping the concentration of Na^+ high in the ECF and the concentration of K^+ high in the ICF.

2 Given the concentration gradients that exist across the plasma membrane, K^+ tends to drive membrane potential to the equilibrium potential for K^+ (–90 mV), whereas Na^+ tends to drive membrane potential to the equilibrium potential for Na^+ (+60 mV).

3 However, K^+ exerts the dominant effect on resting membrane potential because the membrane is more permeable to K^+. As a result, resting potential (–70 mV) is much closer to E_{K^+} than to E_{Na^+}.

4 During the establishment of resting potential, the relatively large net diffusion of K^+ outward does not produce a potential of –90 mV because the resting membrane is slightly permeable to Na^+ and the relatively small net diffusion of Na^+ inward neutralizes (in gray shading) some of the potential that would be created by K^+ alone, bringing resting potential to –70 mV, slightly less than E_{K^+}.

5 The negatively charged intracellular proteins (A^-) that cannot cross the membrane remain unbalanced inside the cell during the net outward movement of the positively charged ions, so the inside of the cell is more negative than the outside.



● **FIGURE 3-23** **Effect of concurrent K^+ and Na^+ movement on establishing the resting membrane potential.**

Membrane Potential

- To understand this concept, **assume** that each separated pair of charges in **Figure below** represents 10 mV of potential. (This is not correct in **reality**, because in **reality** many separated charges must be present to account for a potential of 10 mV.) In this simplified example, 9 separated pluses and minuses, with the minuses on the inside, represent the E_{K+} of -90 mV. Superimposing the slight influence of Na^+ on this K^+-dominated membrane, assume that 2 Na^+ ions **enter** the cell down the Na^+ concentration and electrical gradients (explain??).

Membrane Potential

■ The **inward** movement of **these 2 positively charged Na^+ ions neutralizes** some of the potential established by K^+, so now only 7 pairs of charges are separated, and the potential is

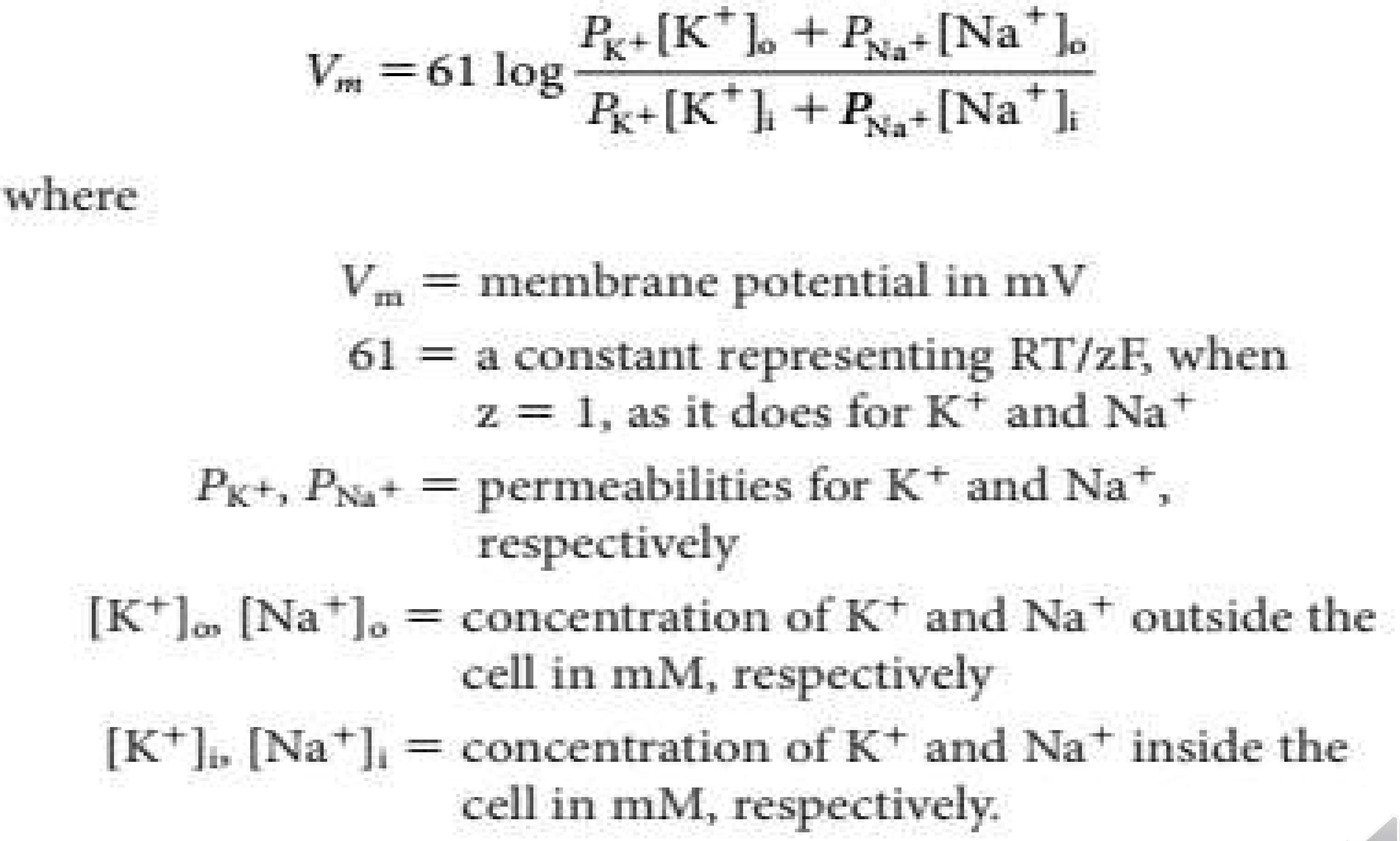
-70 mV. This is **the resting membrane potential** of **a typical nerve cell.** The resting potential is much closer to E_{K+} than to E_{Na+} (Explain??), but it is slightly less than E_{K+} (Explain??).

Membrane Potential

- **Membrane potential** can be calculated using the Goldman-Hodgkin-Katz equation (GHK equation), which takes into account the **relative permeabilities** and **concentration gradients** of **all** permeable ions. The resting membrane is permeable to K^+, $Na^{+,}$ and Cl^-, but Cl^- **does not directly** contribute to potential in **most** cells. Therefore, Cl^- can be ignored when calculating **membrane potential**, making the simplified GHK equation (The GHK equation is an expanded version of the Nernst equation) :

Membrane Potential

- The simplified GHK equation:



$$V_m = 61 \log \frac{P_{K^+}[K^+]_o + P_{Na^+}[Na^+]_o}{P_{K^+}[K^+]_i + P_{Na^+}[Na^+]_i}$$

where

V_m = membrane potential in mV

61 = a constant representing RT/zF, when z = 1, as it does for K^+ and Na^+

P_{K^+}, P_{Na^+} = permeabilities for K^+ and Na^+, respectively

$[K^+]_o$, $[Na^+]_o$ = concentration of K^+ and Na^+ outside the cell in mM, respectively

$[K^+]_i$, $[Na^+]_i$ = concentration of K^+ and Na^+ inside the cell in mM, respectively.

Membrane Potential

- Assuming the resting membrane is 25 times more permeable to K$^+$ than to Na$^+$, then the relative permeabilities are $P_{K+} = 1.0$ and $P_{Na+} = 0.04$ (1/25 of 1.0). Given these permeabilities and the concentrations for K$^+$ and Na$^+$ in the ECF and ICF, so

$$
\begin{aligned}
V_m &= 61 \log \frac{(1)(5) + (0.04)(150)}{(1)(150) + (0.04)(15)} \\
&= 61 \log \frac{5 + 6}{150 + 0.6} \\
&= 61 \log 0.073
\end{aligned}
$$

Because the log of 0.073 is -1.137,

$$V_m = 61\ (-1.137) = -69\ \text{mV}$$

Membrane Potential

- Adding -1 mV of potential generated directly by the Na^+-K^+ pump to 69 mv totals -70 mV for the resting membrane potential.

Membrane Potential

- **Balance** of **passive leaks** and **active pumping** at **resting membrane potential:**
- At **resting potential**, **neither** K^+ nor Na^+ is at **equilibrium.** A potential of -70 mV **does not exactly** counterbalance the concentration gradient for K^+; it takes a potential of -90 mV to do that. Thus, K^+ **slowly continues** to passively **exit** (leaves) through its **leak channels down** this **small** concentration gradient.

Membrane Potential

- **Leak channels** are channels that are **open all the time**, thus permitting **unregulated leakage** of their chosen ion **down** electrochemical gradients. In the case of Na^+, the concentration and electrical gradients **do not** even oppose each other; they **both** favor the inward movement of Na^+. Therefore, Na^+ **continually leaks** inward **down** its electrochemical gradient, but **only slowly** (because of its low permeability, that is, because of the scarcity of Na^+ leak channels).

Membrane Potential

- Because such leaking goes on **all the time**, why doesn't the **intracellular concentration** of **K^+** continue to fall and the concentration of Na^+ inside the cell progressively increase? The reason is that the Na^+-K^+ pump **counterbalances** the **rate** of **passive leakage**. At **resting potential**, this pump transports **back** into the cell essentially the **same number** of **K^+** ions that have **leaked out** and **simultaneously** transports to **the outside** the Na^+ ions that have **leaked in**.

Membrane Potential

■ At **this point**, **a steady state** exists: **No** net movement of any ions takes place, because all passive leaks are exactly balanced by active pumping. Thus, **not only** is the Na^+–K^+ pump initially **responsible** for the Na^+ and K^+ **concentration differences** across the membrane but it also **maintains** these **differences**. Because the **concentration gradients** and **permeabilities** for Na^+ and K^+ remain **constant** in the **resting state**, the RMP **established** by these forces remains **constant**.

Membrane Potential

- **Chloride movement at resting membrane potential:**

- Chloride (Cl^-) is the **principal ECF anion**. Its **equilibrium potential** (E_{Cl-}) is -70 mV (exactly the same as the RMP).

- When the **ionic effects** that could account for the membrane potential was first examined, it was thought that **Cl^- movements** and **establishment** of the **Cl^- equilibrium potential** could be **solely responsible** for producing the RMP.

Membrane Potential

- Actually, the **reverse** is the case. The **membrane potential** is responsible for **driving** the **distribution** of Cl^- across the membrane. **Most** cells are **highly** permeable to Cl^- but have **no active** transport mechanisms for this ion. With **no** active forces acting on it, Cl^- **passively distributes itself** to achieve an individual state of equilibrium. In this case, Cl^- is **driven out** of the cell, establishing an **inward concentration** gradient that **exactly** counterbalances the **outward electrical gradient** (that is, the RMP) produced by K^+ and Na^+ **movement**.

Membrane Potential

- Thus, the **concentration difference** for Cl^- between the ECF and ICF is brought about **passively** by the **presence** of the **membrane potential** rather than **maintained** by an **active pump** (as is the case for K^+ and Na^+). Therefore, in **most** cells, Cl^- **does not influence** RMP; instead, **membrane potential passively influences** the Cl^- **distribution.**

Membrane Potential

- **Specialized use** of **membrane potential** in **nerve** and **muscle cells:**
- Nerve and muscle cells have developed a specialized use for membrane potential. They can rapidly and transiently **alter** their membrane permeabilities to the involved ions in response to appropriate stimulation, thereby bringing about fluctuations in membrane potential. The rapid fluctuations in potential are responsible for producing nerve impulses in nerve cells and for triggering contraction in muscle cells.

Membrane Potential

- Even though all cells display a membrane potential, its **significance** in other cells (cells other than nerve and muscle cells) is **uncertain,** although changes in membrane potential of some secretory cells, for example insulin-secreting cells, have been linked to their level of secretory activity.