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# Quantum Electrochemical Equilibrium: Quantum Version of the Goldman–Hodgkin–Katz Equation

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**Abstract:** The resting membrane voltage of excitable cells such as neurons and muscle cells is determined by the electrochemical equilibrium of potassium and sodium ions. This voltage is calculated by using the Goldman–Hodgkin–Katz equation. However, from the quantum perspective, ions with significant quantum tunneling through closed channels can interfere with the electrochemical equilibrium and affect the value of the membrane voltage. Hence, in this case the equilibrium becomes quantum electrochemical. Therefore, the model of quantum tunneling of ions is used in this study to modify the Goldman–Hodgkin–Katz equation in such a way to calculate the resting membrane voltage at the point of equilibrium. According to the present calculations, it is found that lithium—with its lower mass—shows a significant depolarizing shift in membrane voltage. In addition to this, when the free gating energy of the closed channels decreases, even sodium and potassium ions depolarize the resting membrane voltage via quantum tunneling. This study proposes the concept of quantum electrochemical equilibrium, at which the electrical potential gradient, the concentration gradient and the quantum gradient (due to quantum tunneling) are balanced. Additionally, this concept may be used to solve many issues and problems in which the quantum behavior becomes more influential.

**Keywords:** quantum tunneling; quantum conductance; quantum biology; voltage-gated channel; quantum electrochemical equilibrium

## 1. Introduction

Resting membrane voltage is determined by the electrochemical equilibrium of the ions such as potassium and sodium ions [1]. Recently, several studies have focused on the quantum behavior of ions [2,3] and its implications in the biologic systems including ion channels' selectivity [4–7]. Despite the increasing interest on the quantum transport of ions across the biologic membrane [4–7], the quantum transport of ions through the closed hydrophobic gate of the channels has not been addressed by researchers. Despite that, it has been proposed that ions can use the phenomenon of quantum tunneling to pass through the closed voltage-gated channels of the biologic membrane [8]. Additionally, it has been suggested that quantum tunneling phenomenon can be applicable on ions [9,10]. However, under normal physiological conditions sodium and potassium ions have insignificant tunneling probability that does not affect the electrochemical equilibrium or the membrane voltage [8]. On the other hand, when ions with significant tunneling probability such as lithium ions are introduced to the biologic system, they will affect the resting membrane voltage [8,11]. Therefore, these ions determine the membrane voltage not by the classical electrochemical equilibrium but by quantum electrochemical equilibrium indicating the role of quantum transport through the closed channels via quantum tunneling. The term "quantum electrochemical equilibrium" is novel and it has not been proposed before especially in cell membrane biophysics. Thus, this study proposes new concept that may serve to solve future paradoxes, problems and medical issues such as epilepsy and cardiac arrhythmias caused by channelopathies. This insight will be discussed in this article.

Quantum electrochemical equilibrium is the equilibrium in which the electrical potential gradient, the chemical gradient (concentration gradient) and the quantum gradient (quantum tunneling effect) are balanced. At this equilibrium, the membrane voltage of the membrane will be determined. The plausible indication of positing this concept is to determine the membrane voltage of equilibrium at which the quantum membrane conductance can be calculated. Intriguingly, the quantum membrane conductance depends on the kinetic energy of the ion which also depends on the membrane voltage itself [8]. Therefore, if the biologic system begins with certain value of quantum conductance other than that of equilibrium, the membrane will get certain value of voltage that will change the quantum conductance which in turn will change the membrane voltage and this voltage will change the quantum conductance again, etc. Based on this, the quantum electrochemical equilibrium can be used to determine the value of the membrane voltage at which the quantum conductance cannot change the membrane voltage anymore because at this point all the three gradients (the chemical, the electrical and the quantum) are balanced. In other words, the membrane voltage will be calculated when the net flux of ions due to these three gradients across the membrane is zero. Consequently, this will offer more accurate theoretical results by defining the predicted value of membrane voltage due to quantum electrochemical equilibrium. Additionally, this will be beneficial if experiments are conducted to measure the membrane voltage so that a reliable comparison can be made between the experimental observations and the theoretical data.

The aim of the present study is to modify the Goldman–Hodgkin–Katz equation in a way to integrate the effect of quantum tunneling so that the resting membrane potential can be calculated at the equilibrium point. This integration is accomplished by using the model of quantum tunneling of ions [8]. Additionally, the present study will modify some aspects of the mathematical model used before [8] and the model used to explain the therapeutic effect of lithium [11] to ensure higher accuracy in the obtained results and the calculations will be based on defining the state of equilibrium. Moreover, different reasonable assumptions are made to show how the concept of quantum electrochemical equilibrium can be used to delineate the effect of certain pathologies on the membrane potential.

## 2. Methods

The model of quantum tunneling of ions through the closed voltage-gated channels was proposed. In this model, the intracellular hydrophobic gate is defined as an energy barrier and ions have the opportunity to pass through [8]. Hence, the quantum conductance can be calculated and used to investigate the effect of quantum tunneling on the membrane potential.

The intracellular hydrophobic gate impends the passage of ions because it forms barrier energy higher than the kinetic energy *KE* of moving ions. This barrier energy is referred to the free gating energy of the channel *G* which represents the minimum amount of energy required to open the closed gate [8,12,13]. In addition to this, if the closed gate is delineated as a potential barrier, its shape will not be rectangular where barrier energy is constant at every point, but it will change as ion passes across the gate. This is because the free gating energy *G* represents the total sum of energy amount that ion should acquire to overcome the barrier and this energy is divided on each point or position *x* in the gate. Consequently, as ion goes through each position *x*, it needs certain quantity of energy $U(x)$ that enables it to pass starting from a position *X1* where $U(x) = KE$ until reaching the end of the gate *X2*. Therefore, the general formula of tunneling probability or transmission coefficient of ions *(P)*, as derived from Schrodinger equation, can be written as the following [8,14]:

$$P = e^{\frac{-\sqrt{8m}}{\hbar} \int_{X1}^{X2} \sqrt{U(x)-KE}\,dx} \tag{1}$$

where *m* is the mass of the ion, $\hbar$ is the reduced Planck constant ($1.05 \times 10^{-34}$ Js) and X1–X2 is the region where $U(x)$ is equal or higher than *KE*.

To solve the integral in Equation (1), a mathematical relation between $U(x)$ and $x$ must be set. To do so, the closed gate is demonstrated as regular electric field $E$ in the space of a parallel capacitor which holds out against the movement of ions [8]. This capacitor will have a voltage $V$ and a length $L$ which also represents the length of the intracellular hydrophobic gate [8]. Thus, the electric field $E$ corresponded to the closed gate can be formulated as in the following equation [8]:

$$E = \frac{V}{L} = \frac{G}{qL} \tag{2}$$

where $q$ is the charge of the ion.

Additionally, $U(x)$ can be calculated by the following equation [8]:

$$U(x) = qEx \tag{3}$$

Eventually, by substituting Equation (2) in Equation (3), the equation becomes:

$$U(x) = \frac{G}{L}x \tag{4}$$

Equation (4) can be substituted in Equation (1) to become:

$$P = e^{-\frac{\sqrt{8m}}{\hbar} \int_{X1}^{X2} \sqrt{\frac{G}{L}x - KE}dx} \tag{5}$$

The integral in Equation (5) can be solved as the following:

$$\int_{X1}^{X2} \sqrt{\frac{G}{L}x - KE}dx = \frac{2L}{3G}\sqrt{\left(\frac{G}{L}x_2 - KE\right)^3} - \frac{2L}{3G}\sqrt{\left(\frac{G}{L}x_1 - KE\right)^3} \tag{6}$$

As previously said, $X2$ is at the end of the gate which means $X2 = L$ and $X1$ is where $U(x) = KE$. Therefore, Equation (6) becomes:

$$\int_{X1}^{X2} \sqrt{\frac{G}{L}x - KE}dx = \frac{2L}{3G}\sqrt{(G - KE)^3} \tag{7}$$

By substituting Equation (7) in Equation (5), the equation of tunneling probability becomes:

$$P = e^{-\frac{\sqrt{8m}}{\hbar} \times \frac{2L}{3G}\sqrt{(G-KE)^3}} \tag{8}$$

To determine the effect of ions quantum tunneling on the resting membrane voltage, the membrane conductance due to quantum tunneling (quantum conductance) $C_{QM}$ must be calculated.

To calculate $C_{QM}$, quantum conductance of single closed channel $C_{Q-channel}$ must be considered. Assuming that there is no spin degeneracy of ions, $C_{Q-channel}$ can be calculated by the following equation [14,15]:

$$C_{Q-channel} = \frac{10^3 q^2}{h}P \tag{9}$$

where $q$ is the charge of the ion, $h$ is the Planck constant ($6.6 \times 10^{-34}$ Js), $P$ is the tunneling probability and $10^3$ is used to convert the unit of conductance from Siemens (S) to milliSiemens (mS).

Finally, taking into consideration the density of channels $D$ which is the number of channels per area unit of the membrane (channels/cm$^2$), $C_{QM}$ can be calculated [8]:

$$C_{QM} = C_{Q-channel} \times D \tag{10}$$

The kinetic energy of ions is due to the membrane voltage and the thermal source of body temperature. Therefore, as long as the membrane is polarized (negative inside in comparison to the outside) and the hydrophobic gate is located at the intracellular end of the membrane [16,17], the extracellular cations get kinetic energy while passing through the membrane voltage and kinetic energy from the thermal source, but the intracellular cations get kinetic energy only from the thermal source because they will hit the intracellular hydrophobic gate before going through the membrane voltage. Therefore, the kinetic energy of extracellular $KE_o$ and intracellular $KE_i$ cations can be calculated by the following equations, respectively [18]:

$$KE_o = qV_m + \frac{1}{2}K_BT \tag{11}$$

$$KE_i = \frac{1}{2}K_BT \tag{12}$$

where $q$ is the charge of the ion, $V_m$ the membrane potential (voltage), $K_B$ is the Boltzmann's constant ($1.38 \times 10^{-23}$ J/K) and $T$ is the absolute body temperature (310 K).

As presented in the Equations (11) and (12), it is apparent that extracellular cations acquire higher kinetic energy when compared with intracellular cations.

The intracellular hydrophobic gate of the voltage-gated channels such as sodium and potassium channels represents the main controller of the channels' conductance unlike the selectivity filter which aims to differentiate between ions with minor effect on the channels' conductance for the specific ion [12,13,16,17]. For this reason, the quantum model is applied on this gate to calculate the quantum conductance of the channel and to determine the effect of quantum tunneling of ions through the closed gate on the membrane voltage.

Taking into consideration the classical electrochemical contribution of potassium and sodium ions and the significant quantum tunneling of a monovalent cation X such as lithium, the Goldman–Hodgkin–Katz equation can be written as the following:

$$C_{Na}[Na]_o + C_K[K]_o + C_{QM(Xo)}[X]_o = e^{\frac{FV_m}{RT}}(C_{Na}[Na]_i + C_K[K]_i + C_{QM(Xi)}[X]_i) \tag{13}$$

where ($o$) means extracellular, ($i$) means intracellular, [ ] is the concentration, $C_{Na}$ is the membrane conductance of sodium at the resting state, $C_K$ is the membrane conductance of potassium at the resting state, $V_m$ is the membrane voltage, $F$ is Faraday's constant (96,485.33 C/mol), $R$ is the gas constant (8.31 J/Kmol) and $T$ is the absolute body temperature (310 K).

By substituting Equations (8)–(12) in Equation (13):

$$C_{Na}[Na]_o + C_K[K]_o + Ae^{B\sqrt{(G-(qV_m+\frac{1}{2}K_BT))^3}}[X]_o = e^{\frac{-FV_m}{RT}}(C_{Na}[Na]_i + C_K[K]_i + Ae^{B\sqrt{(G-\frac{1}{2}K_BT)^3}}[X]_i) \tag{14}$$

where $A = 10^3 D\frac{q^2}{h}$ and $B = \frac{-\sqrt{8m}}{\hbar} \times \frac{2L}{3G}$

Equation (14) calculates the resting membrane voltage $V_m$ that is negative inside in comparison to the outside of the cell. The non-quantum conditions at the resting state favor the polarized state of the membrane as being negative inside in comparison to the outside. Thus, the quantum tunneling effect does not switch the polarization of the membrane to become positive inside in comparison to the outside, but it changes the value of polarization. Furthermore, $V_m$ in the equation represents the absolute value of the voltage, for this reason the negative sign is added in this expression $e^{\frac{-FV_m}{RT}}$.

In a conclusion, Equation (14) calculates the absolute value of the resting membrane voltage, which is negative inside in comparison to the outside, governed by the quantum electrochemical equilibrium.

Interestingly, the quantum electrochemical equilibrium of sodium and potassium ions can be significant and affect the membrane voltage when the factors that determine the tunneling probability change. Thus, the following general equation can be used to calculate the membrane voltage at the equilibrium point when the quantum tunneling of sodium and potassium ions are more evident than in normal physiology:

$$(C_{Na} + C_{QM(Na)o})[Na]_o + (C_K + C_{QM(K)o})[K]_o = e^{\frac{FV_m}{RT}}((C_{Na} + C_{QM(Na)i})[Na]_i + (C_K + C_{QM(K)i})[K]_i) \quad (15)$$

The quantum conductance for intracellular sodium and potassium ions can be neglected because they have lower kinetic energy that makes the tunneling probability and the quantum conductance low in a way that they do not affect the membrane voltage. Accordingly—and by substituting Equations (8)–(12) for sodium and potassium ions in Equation (15)—the equation can be written as the following:

$$(C_{Na} + [Ae^{B\sqrt{(G-(qV_m+\frac{1}{2}K_BT))^3}}]_{Na})[Na]_o + (C_K + [Ae^{B\sqrt{(G-(qV_m+\frac{1}{2}K_BT))^3}}]_K)[K]_o = e^{\frac{-FV_m}{RT}}(C_{Na}[Na]_i + C_K[K]_i) \quad (16)$$

Moreover, if the focus is on sodium ions only, the equation can be written as the following:

$$(C_{Na} + [Ae^{B\sqrt{(G-(qV_m+\frac{1}{2}K_BT))^3}}]_{Na})[Na]_o + C_K[K]_o = e^{\frac{-FV_m}{RT}}(C_{Na}[Na]_i + C_K[K]_i) \quad (17)$$

On the other hand, if the focus is on potassium ions only, the equation can be written as the following:

$$C_{Na}[Na]_o + (C_K + [Ae^{B\sqrt{(G-(qV_m+\frac{1}{2}K_BT))^3}}]_K)[K]_o = e^{\frac{-FV_m}{RT}}(C_{Na}[Na]_i + C_K[K]_i) \quad (18)$$

## 3. Results and Discussion

The resting membrane potential is set when the electrochemical equilibrium has been established and it is calculated by the Goldman–Hodgkin–Katz equation. However, when an ion with significant quantum conductance is introduced into the biologic environment, the resting membrane potential cannot be calculated by the same equation and further modifications are required to determine the effect of quantum tunneling on the resting membrane potential. The Equations (14)–(18) represent the modified equations required to calculate the membrane voltage at the quantum electrochemical equilibrium.

### 3.1. Quantum Electrochemical Equilibrium under the Effect of Lithium Ions

Lithium has significant quantum tunneling effect and significant quantum conductance [8,11]. Therefore, it is used to be the ion X in Equation (14), also the model is applied on the sodium voltage-gated channels because they are approximately selective for lithium as for sodium [19].

By substituting 0.005 mS/cm² [1], 0.5 mS/cm² [1], 142 mmol/L [1], 14 mmol/L [1], 4 mmol/L [1], 140 mmol/L [1], 0.9 mmol/L [11,20], 3.6 mmol/L [11,20], $1.6 \times 10^{-19}$ C, $1.15 \times 10^{-26}$ kg, $5.4 \times 10^{-11}$ m [8,21], $6.33 \times 10^{-20}$ J [18], $5 \times 10^9$ channels/cm² [22] for the following variables $C_{Na}$, $C_K$, $[Na]_o$, $[Na]_i$, $[K]_o$, $[K]_i$, $[Li]_o$, $[Li]_i$, the lithium ion's charge ($q$), the mass of lithium ion ($m$), the length of the gate ($L$), the free gating energy ($G$) and the channels density in the neuronal membrane ($D$), respectively in Equation (14):

$$2.71 + 1.75 \times 10^8 e^{-1.64\sqrt{(6.12-16V_m)^3}} = 70.08 e^{-37.45V_m} \quad (19)$$

Using MATLAB software, Equation (19) can be solved and $V_m = 71$ mV.

Accordingly, the resting membrane voltage becomes −71 mV (negative inside in comparison to the outside of the cell) under the effect of quantum tunneling of lithium ions. Before adding lithium ions, the resting membrane voltage is −87 mV and that means lithium ions show a depolarization effect on the membrane potential. Here is a clear example on how the quantum behavior of ions can really affect the membrane voltage of the cells using the concept of quantum electrochemical equilibrium.

Based on the membrane voltage of −71 mV, the tunneling probability and the quantum membrane conductance of lithium ions can be calculated using the Equations (8)–(12). See Table 1.

**Table 1.** Tunneling probability and the quantum membrane conductance of lithium ions when the membrane voltage is −71 mV.

| Lithium | Tunneling Probability | Quantum Membrane Conductance (mS/cm$^2$) |
|---|---|---|
| Extracellular | $1.22 \times 10^{-8}$ | 2.37 |
| Intracellular | $1.65 \times 10^{-11}$ | $3.2 \times 10^{-3}$ |

Two interesting findings have been found in experiments documented in the literature. First, lithium ions depolarize the resting membrane potential, for example, from −74.9 mV to −48.64 mV at extracellular concentration of 100 mmol/L and intracellular concentration of 120 mmol/L after 1 h of infusion of lithium salt [23]. Second, lithium ions have high permeability at the resting state which is a contributing factor to the depolarization induced by lithium ions [23]. The classical electrophysiology cannot provide a reasonable solution for this issue because the high lithium conductance cannot be explained since lithium passes approximately by the same high degree of selectivity of sodium through sodium channels [19]; however, it passes by the same low selectivity of sodium through the potassium channels [24]. This means that lithium will have a conductance approximately equals to that for sodium at the resting state which is 0.005 mS/cm$^2$ and this conductance is not enough to cause such marked depolarization at the extracellular concentration of 100 mmol/L and intracellular concentration of 120 mmol/L. Paradoxically, these concentrations after 1 h should induce hyperpolarization instead of depolarization because it is obvious that intracellular concentration is higher than the extracellular concentration and this means that lithium ions will flow from inside the cell to the outside resulting in hyperpolarization. However, the experimental observations are consistent with membrane depolarization instead of hyperpolarization and this can be only true if the extracellular lithium ions have higher conductance than the intracellular ions. Based on the values in Table 1, it is evident that extracellular lithium ions have higher quantum conductance in comparison with the intracellular lithium ions and this attributed to the higher kinetic energy of extracellular ions which results in higher quantum tunneling probability. Thus, the quantum model provides congruous clarification of the discrepancy of conductance between extracellular and intracellular lithium ions.

According to the results obtained in Table 1, it is clear that extracellular lithium has quantum membrane conductance higher than the resting conductance of sodium and even higher than that of potassium. This high quantum conductance of lithium can resolve the issue of the ability of lithium to depolarize the resting membrane potential with high resting conductance. Furthermore, if the extracellular concentration of 100 mmol/L and the intracellular lithium concentration of 120 mmol/L are substituted in Equation (14), the membrane voltage will be −39 mV which represents marked depolarization. Moreover, another similar experiment was conducted to show a depolarization from −84.6 mV to −59.2 mV after 1 h of lithium salt infusion [23]. Probably, if the infusion persisted for longer than 1 h in these two experiments, the membrane voltage would be −39 mV.

These set of equations will be useful when the different variables (i.e., the free gating energy, the kinetic energy of the ion, the length of the gate and the mass of the ion) that govern the tunneling probability are changed under different pathological conditions because when they change, the tunneling probability may change significantly in a way that affects the resting membrane potential. Therefore, establishing equations that calculate the membrane potential at the point of equilibrium is

important to explore the effect of such changes on the membrane voltage and consequently on the overall electrophysiological features of the biologic membrane.

Possible mechanism that may decrease the free gating energy of the channel is the disorder of channelopathies [25–27]. This disorder is implicated in different pathologies including epilepsy and cardiac arrhythmias [28]. In the further calculations, it will be shown how such decrease in the free gating energy can make the quantum tunneling more obvious for sodium and potassium ions.

### 3.2. Quantum Electrochemical Equilibrium when the Free Gating Energy of the Sodium Channels Decreases

Regarding sodium ions, the same values substituted for lithium will be substituted for sodium taking into consideration the differences in concentration and mass (mass of sodium is $3.8 \times 10^{-26}$ kg):

1. At normal physiological parameters with no decrease in the free gating energy and by substituting in Equation (17), the equation becomes:

$$2.71 + 2.75 \times 10^{10} e^{-2.99 \sqrt{(6.12 - 16 V_m)^3}} = 70.07 e^{-37.45 V_m} \tag{20}$$

By using MATLAB software, $V_m = 87$ mV and this indicates that sodium ions do not affect the membrane voltage under normal physiological parameters so that their equilibrium is mainly governed by the classical electrochemical equilibrium.

Based on the membrane voltage of −87 mV and no change in the free gating energy, the quantum tunneling probability and the quantum membrane conductance of sodium ions can be calculated. See Table 2.

**Table 2.** Tunneling probability and the quantum membrane conductance of sodium ions with membrane voltage of −87 mV and no change in the free gating energy.

| Sodium | Tunneling Probability | Quantum Membrane Conductance (mS/cm$^2$) |
|:---:|:---:|:---:|
| Extracellular | $4.33 \times 10^{-14}$ | $8.4 \times 10^{-6}$ |
| Intracellular | $2.19 \times 10^{-20}$ | $4.25 \times 10^{-12}$ |

The quantum conductance of extracellular sodium ions is lower than their conductance at the resting state (0.005 mS/cm$^2$) and this explains why membrane voltage does not change due to quantum tunneling of sodium ions under normal physiological parameters. The quantum conductance of intracellular sodium ions is much lower than the quantum conductance of extracellular sodium ions and the conductance at the resting state (0.005 mS/cm$^2$) and hence it was neglected when the membrane voltage was calculated.

2. Assuming that a disorder such as channelopathy affects the voltage-gated sodium channels and decreases the free gating energy by 25% so that the barrier energy becomes $4.75 \times 10^{-20}$ J after being $6.33 \times 10^{-20}$ J, the equation becomes:

$$2.71 + 2.75 \times 10^{10} e^{-3.98 \sqrt{(4.54 - 16 V_m)^3}} = 70.07 e^{-37.45 V_m} \tag{21}$$

Using MATLAB software, $V_m = 77$ mV and this means depolarizing shift in the membrane voltage from −87 mV to −77 mV.

Based on the membrane voltage of −77 mV and the decrease in the free gating energy, the tunneling probability and the quantum membrane conductance can be calculated. See Table 3.

**Table 3.** Tunneling probability and the quantum membrane conductance of sodium ions with membrane voltage of −77 mV and decrease in the free gating energy by 25%.

| Sodium | Tunneling Probability | Quantum Membrane Conductance (mS/cm$^2$) |
|---|---|---|
| Extracellular | $3.93 \times 10^{-11}$ | $7.62 \times 10^{-3}$ |
| Intracellular | $1.92 \times 10^{-17}$ | $3.72 \times 10^{-9}$ |

The quantum conductance of extracellular sodium ions is higher than the conductance at the resting state (0.005 mS/cm$^2$) and this interprets the depolarizing shift in the membrane voltage. In addition to this, the quantum conductance of intracellular sodium ions is still low in a way that does not affect the membrane voltage.

3. If the calculation is repeated with a decrease by 50% in the free gating energy so that the barrier energy drops to $3.17 \times 10^{-20}$ J, the equation becomes:

$$2.71 + 2.75 \times 10^{10} e^{-5.99 \sqrt{(2.96 - 16V_m)^3}} = 70.07 e^{-37.45V_m} \tag{22}$$

By using MATLAB software, $V_m = 39$ mV and this indicates depolarizing shift from −87 mV to −39 mV.

Based on the membrane voltage of −39 mV and the decrease in the free gating energy, the tunneling probability and the quantum membrane conductance can be calculated. See Table 4.

**Table 4.** Tunneling probability and the quantum membrane conductance with membrane voltage of −39 mV and decrease in the free gating energy by 50%.

| Sodium | Tunneling Probability | Quantum Membrane Conductance (mS/cm$^2$) |
|---|---|---|
| Extracellular | $5.0 \times 10^{-10}$ | $9.7 \times 10^{-2}$ |
| Intracellular | $5.4 \times 10^{-14}$ | $1.05 \times 10^{-5}$ |

Here, the depolarizing shift is larger than the previous one because the quantum tunneling probability and the quantum conductance are higher. Again, quantum conductance of intracellular sodium ions is still low and does not affect the membrane voltage.

*3.3. Quantum Electrochemical Equilibrium when the Free Fating Energy of the Potassium Channels Decreases*

Regarding potassium ions and their selective channels, the following values will be considered for substitution in Equation (18): the free gating energy is $5.35 \times 10^{-20}$ J [29], the length of the gate is $4.4 \times 10^{-11}$ m [8,21] and the mass is $6.5 \times 10^{-26}$ kg:

1. At normal physiological parameters, the equation will be:

$$2.71 + 7.76 \times 10^8 e^{-3.76 \sqrt{(5.14 - 16V_m)^3}} = 70.07 e^{-37.45V_m} \tag{23}$$

By using MATLAB software, $V_m = 87$ mV and this indicates that the quantum tunneling of potassium does not affect the membrane voltage.

Based on the membrane voltage of −87 mV and no decrease in the free gating energy, the quantum tunneling probability and the quantum membrane conductance can be calculated. See Table 5.

**Table 5.** Tunneling probability and the quantum membrane conductance of potassium ions with membrane voltage of −87 mV and no change in the free gating energy.

| Potassium | Tunneling Probability | Quantum Membrane Conductance (mS/cm$^2$) |
|---|---|---|
| Extracellular | $1.39 \times 10^{-12}$ | $2.7 \times 10^{-4}$ |
| Intracellular | $8.6 \times 10^{-20}$ | $1.67 \times 10^{-11}$ |

The quantum conductance of extracellular potassium ions is lower than the resting conductance of potassium (0.5 mS/cm$^2$) and sodium (0.005 mS/cm$^2$) and this gives the reason why quantum tunneling of potassium ions does not affect the membrane voltage under normal physiological conditions. Moreover, the quantum conductance of intracellular potassium ions is much lower than the quantum conductance of extracellular potassium ions and the resting conductance and hence it was neglected when the membrane voltage was calculated.

2. If the free gating energy decreases by 25%, the equation will be:

$$2.71 + 7.76 \times 10^8 e^{-5.02 \sqrt{(3.8-16V_m)^3}} = 70.07 e^{-37.45 V_m} \tag{24}$$

Then, $V_m = 78$ mV, and this shows depolarizing shift in the membrane voltage from −87 mV to −78 mV.

Based on the membrane voltage of −78 mV and the decrease in the free gating energy, the tunneling probability and the quantum membrane conductance can be calculated. See Table 6.

**Table 6.** Tunneling probability and the quantum membrane conductance of potassium ions with membrane voltage of −78 mV and decrease in the free gating energy by 25%.

| Potassium | Tunneling Probability | Quantum Membrane Conductance (mS/cm$^2$) |
|---|---|---|
| Extracellular | $1.34 \times 10^{-9}$ | 0.26 |
| Intracellular | $6.99 \times 10^{-17}$ | $1.36 \times 10^{-8}$ |

The quantum membrane conductance of extracellular potassium ions is comparable to the resting conductance of potassium ions (0.5 mS/cm$^2$) and this explains the depolarizing shift. Regarding the quantum conductance of intracellular potassium ions, it is still low and does not influence the membrane voltage.

3. If the free gating energy decreases by 50%, the equation will be:

$$2.71 + 7.76 \times 10^8 e^{-7.56 \sqrt{(2.47-16V_m)^3}} = 70.07 e^{-37.45 V_m} \tag{25}$$

Then, $V_m = 43$ mV and this represents depolarizing shift from −87 mV to −43 mV.

Based on the membrane voltage of −43 mV and the decrease in the free gating energy, the tunneling probability and the quantum membrane conductance can be calculated. See Table 7.

**Table 7.** Tunneling probability and the quantum membrane conductance of potassium ions with membrane voltage of −43 mV and decrease in the free gating energy by 50%.

| Potassium | Tunneling Probability | Quantum Membrane Conductance (mS/cm$^2$) |
|---|---|---|
| Extracellular | $1.54 \times 10^{-8}$ | 2.99 |
| Intracellular | $1.83 \times 10^{-13}$ | $3.55 \times 10^{-5}$ |

Here, the depolarizing shift is larger because the tunneling probability and the quantum conductance of extracellular potassium ions are higher. On the other hand, the quantum membrane conductance of intracellular potassium ions is still low and does not change the membrane voltage.

By comparing the values previously obtained, the quantum tunneling of sodium and potassium ions does not affect the membrane voltage under normal physiology. However, when a decrease in the free gating energy happens due to certain diseases such as channelopathies, the tunneling probability may be significant and affect the membrane voltage due to the significant quantum membrane conductance. Obviously, the exponential function of tunneling probability is sensitive to the decrease in the free gating energy. This sensitivity is manifested in the significant shift in membrane voltage when a drop by 25% and 50% happens to the free gating energy of the voltage-gated

channels. Surprisingly, potassium ions induce depolarizing shift instead of hyperpolarizing shift because the quantum tunneling probability of extracellular potassium ions is much higher than that for intracellular potassium ions since the extracellular ions have higher kinetic energy. Consequently, there will be a net quantum flux of cations to inside the cell resulting in depolarization. Remarkably, lithium can depolarize the membrane voltage under normal physiological parameters unlike sodium and potassium ions which make this action under pathological conditions such as channelopathies or probably any condition that may change the factors that set the tunneling probability. This variance is attributed mainly to the smaller mass of lithium when compared with the mass of sodium and potassium ions.

Furthermore, the discrepancy in the kinetic energy between intracellular and extracellular ions as indicated in the Equations (11) and (12) creates quantum gradient generated from the higher tunneling probability of extracellular ions and the lower tunneling probability of intracellular ions. As a result, a quantum flux of ions from the extracellular space to the intracellular space (inward flux) is created. This quantum inward flux will be balanced with the flux due to the concentration gradient of ions and the flux due to the membrane potential (voltage). At this balance, the net flux of ions across the membrane is zero as presented by the modified Goldman–Hodgkin–Katz equations.

According to the assumptions, when the voltage-gated channels are diseased by channelopathy and the free gating energy decreases, the tunneling probability and quantum conductance increase and the membrane potential is depolarized. The membrane depolarization is a predisposing factor for the hyperexcitability of epilepsy and cardiac arrhythmias. Therefore, the concept of quantum electrochemical equilibrium may be useful to treat such diseases in the future.

The model of quantum tunneling of ions seems to be able to unravel the underlying mechanism behind the ionic current permeated through closed channels as documented in the literature especially that no mechanical opening of the closed gate was observed [30,31]. These currents could be quantum currents generated by quantum tunneling of ions. Accordingly, if experiments will be conducted so that they will measure these quantum currents, the quantum conductance, and the membrane voltage and then a comparison will be made between these experimental observations with the theoretical data postulated here in this article, a consistent correlation may be made to prove the validity of the ions quantum tunneling model.

## 4. Conclusions

The present work introduces a new concept in cell membrane biophysics and this concept is quantum electrochemical equilibrium at which the electrical potential gradient, the concentration gradient and the quantum gradient (due to quantum tunneling effect) are balanced. This concept will be useful to explore the changes on the membrane voltage and the overall excitability when the quantum behavior of ions becomes evident and more obvious under the influence of certain disorders and diseases. Moreover, experiments will be required to prove the validity of the model proposed in this article.

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