Effects of the Experiment Conditions on the Nerve Action Potential: A Model Study

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Abstract: Like electrical wires, neurons were recognized to convey information from one part of the body to another in the form of electricity. Due to its electrical nature, this transmission is very much dependent on the ions around their membranes. As in the case of all electrical messages of the nervous system, the action potential is a membrane potential change caused by the flow of ions through ionic channels in the membrane. With the help of the action potential simulation we test the effect of extracellular ion concentrations on the myelinated single nerve fiber action potential. Tests were designed to mimic the hypo/hyperkalemic and hypo/hypernatremic conditions. Our simulation results have shown that sodium ion channel conductivity is much more susceptible to the changes in the extracellular ion concentrations. Due to more susceptible nature of the sodium channel conductivity –with respect to potassium-, hypo/hyperkalemic conditions are much more dangerous for patients at least for neuronal conduction.

Keywords: Axonal action potential, Conductivity, Ion concentration, Ion channel, Simulation.

INTRODUCTION

Since the environmental conditions effects the living organisms it is wise to assume them with their environment as a whole. Through their receptors mechanical, thermal or chemical stimulus's that were produced by their environments are detected as electrical signals. Later then these signals are transferred to central nervous system in order for the production of the vitally important reflexes and/or decisions [1].

Nerve system carries this electrically coded information throughout the body [2] through neurons. Independent of the stimulus type, whenever a neuron is innervated they produce all or none character voltage changes that we so called action potential (AP). What we know about the single nerve fiber AP mostly came from the Hodgkin and Huxley experimental data that was carried on the squid axon [3].

Under physiological conditions with the dictation of sodium-potassium pump, sodium ion concentration ($[Na^+]$) dominantly found in extracellular while potassium ion concentration ($[K^+]$) dominantly found in the intracellular space. So at rest neurons have resting membrane potential nearly around –70 mV. During AP, change in the conductance's of the ion channels -in a voltage sensitive manner- also change this measured potential difference across the cell membrane.

Majority of the knowledge about the pathologies and the treatment strategies about the human biology come from the experimental model studies that were carried on the genetically homolog animals. Even if for the higher homologies, the results that were obtained from the animals cannot be applied to homo-sapiens. Indeed, there are no such criteria and the data about the fitting of the experimental animal results to human. The other problem on this issue is that whether the experimental models reflect the clinical situation or not? At this point age, gender, body weight, species, body temperature of the experimental animals and the environmental factors must be taken into account [4-6].

In its simplest saying, simulations defined as the building of the representation of the real systems. On the other hand the computer simulations are the transformations of the real world events into the computer's language. In order for the problem solving issue, simulation servers as a powerful tool that's why it became so common. Besides many other advantages simulations provides new research policies, parameters and provides new working conditions on the working system. This new conditions even can be one that cannot be testable on the living systems.

Due to technical limitations, in contrary to the other excitable tissues, it is so difficult to obtain myelinated axonal APs and the ion channel conductivities that were contributed to formation of this potential change. With the aid of axonal stimulation we test the effect of extracellular ion concentration (Na^+ and K^+) changes on the axonal APs and the ion channel's conductance.

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MATERIAL AND METHODS

Under physiological conditions neuronal APs, ionic currents and ion channel conductance (sodium and potassium) were measured and saved on the hard disk of the computer for further analysis. These measurements were accepted as the control conditions for the tested extracellular conditions.

The following equation was used for the time dependent calculations of the AP curves

$$E_m = \frac{RT}{F} ln \frac{P_K[K]_{out} + P_{Na}[Na]_{out} + P_{Cl}[Cl]_{in}}{P_K[K]_{in} + P_{Na}[Na]_{in} + P_{Cl}[Cl]_{out}}$$

where R is the universal gas constant, T is the temperature in Kelvin and F is the Faraday constant. With this equation, it is possible to calculate the voltage of the cell membrane at any time by using the permeability of the membrane (P) and the ionic concentration ([ ])[7-9].

The states of the sodium ion channels used for the simulation summarized in Figure **1**. In this figure, alpha (α) and beta (β) parameters represent the reaction kinetics as an exponential function of the voltage across the membrane. At equilibrium, activations were calculated using the formula: n=α/(α+β), whereas the following is used for time constant T_n=1/(α+β). It is important to note that potassium channels have an only one activation parameter.

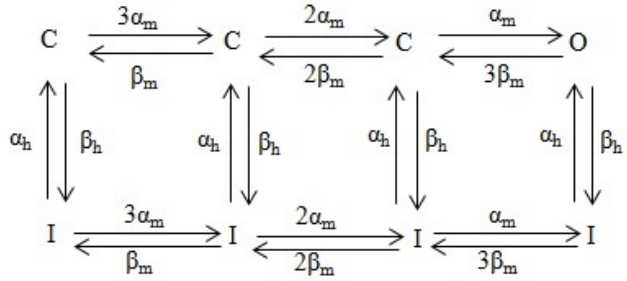

Figure 1: Markov model of the voltage gated sodium channels. Sodium channel has three conformational state: closed (C), open (O), inactivated (I). Transitions between the states are reversible and all transitons have a rate constant. Sodium channels have three activations (m) and an inactivation (h) gates.

On the other hand, sodium channels have activation (m) and inactivation (h) parameters. Similar to activation calculations equilibrium inactivation was calculated by $h=\alpha_h/(\alpha_h+\beta_h)$, and time constant of inactivation was calculated by $T_h=1/(\alpha_h+\beta_h)$.

Sodium channel currents and the reaction rate constants of the cell membrane at any moment

$$I_{Na} = g_{Na} m^3 h (E - E_{Na})$$

$$\alpha_m = \frac{-0,1*(E+35)}{e^{-0,1*(E+35)} - 1}$$

$$\beta_m = 4 * e^{\frac{E+60}{18}}$$

$$\alpha_h = 0,07 * e^{\frac{E+60}{20}}$$

$$\beta_h = \frac{1}{e^{-0,1*(E+30)} + 1}$$

were calculated in accordance with the literature where g is the conductivity, m is the activation, h is the inactivation, E is the voltage across the membrane, and E_{Na} is the Nernst potential [3].

Markov model of the states (open-closed) of the potassium channel is given in Figure **2**. To calculate the potassium channel currents and rate constants following equations are used.

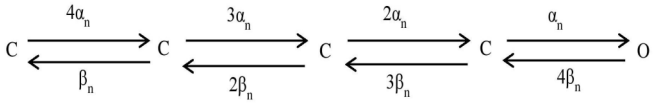

Figure 2: Markov model of the voltage gated potassium channels. Potassium channel has two conformational state: closed (C), open (O). Transitions between the states are reversible and all transitons have a rate constant. Potassium channels have four activation (n) gates.

$$I_K = g_K n^4 (E - E_K)$$

$$\alpha_n = \frac{-0.01*(E+50)}{e^{(-0.1*(E+50))} - 1}$$

$$\beta_n = 0.125 * e^{-\frac{E+60}{80}}$$

To obtain the first data set extracellular sodium concentration ($[Na]_o$) (125, 142 and 160 mM) was changed and measurements were repeated for different axon diameters((μm): 430, 515, 520, 533, 542 and 605). Similarly for the second data set the extracellular potassium ($[K]_o$) concentrations –in accordance with the literature– has chosen as 3, 4 and 6 mM [10, 11]. The control sodium concentration was 142 mM. Applied stimulus amplitude was 30 mV and the injected current charge was 3.58 nanoQ. Simulation parameters of the data sets are given in Table **1**.

With the given conditions in Table **1** simulation was performed and single fiber AP, current and conductivities were recorded on the hard disk of the computer and analyzed with specially designed Microsoft Excel worksheet.

Table 1: Proposed Ionic Molarities for Experimental Conditions

	Condition 1		Condition 2	
	Constants (mM)	**Varying (mM)**	**Constants (mM)**	**Varying (mM)**
$[Na]_o$		125, 142 & 160	142	
$[Na]_i$	10		10	
$[K]_o$	4			3, 4 & 6
$[K]_i$	120		120	
P_{Na}/P_K	0,048		0,048	

Recorded APs are converted to excel compatible format and by using specially designed excel sheet resting membrane potentials, maximum depolarization and time to peak values were calculated for both tested conditions. Additionally, AP duration (APD) at %25 (APD25), %50 (APD50), %75 (APD75) and %90 (APD90) of the repolarization phase were also measured.

For all currents maximum current value and time to peak values were calculated. For conductivities, with a specially designed calculation file maximum conductivity, kinetics of up and down phase and the area under the conductivity curves was calculated.

RESULTS

Capacitance measurement is a frequently used technique in electrophysiological measurements and/or calculations. These measurements reflect the charge storage ability of the cell membrane which is proportional to the cell size. Quantitative expression of current except single channel measurements is given by the ratio of the current to the capacitance of the cell. In physiological limits for a neuron the calculated capacitances for different axon diameter is given in Figure **3**. Since there are many different factors on the relationship, data are fitted and the linear relationship is found (R^2=0,9). Calculated capacitance values of the axons are between 0,08 and 0,14 µF, of which diameter varied from 430 to 675 µm.

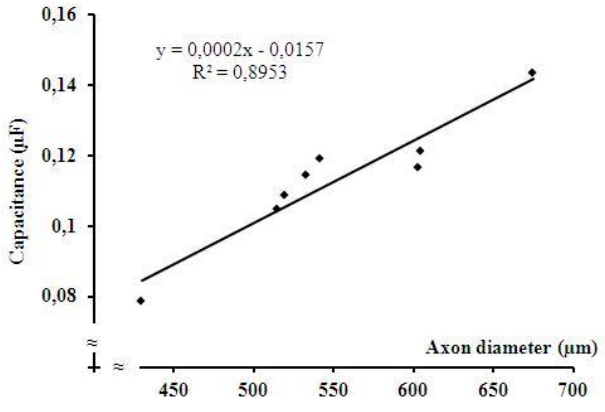

Figure 3: Axon diameter vs capacitance. Under physiological conditions capacitances, the charge storage ability of the axon, of the axons are given, The diameter of the axons used was between 430 and 675 µm.

Since the axon capacitance is related to the areas, for the both suggested conditions it is obvious that the capacitance of the axons did not to change with extracellular ionic concentration (Na^+ and K^+).

Although the measurement on the single fiber AP is relatively macroscopic it can be used as a functional tool to understand and assess the function of the nerve. Moreover, it is useful not only to explore the physiology of the nerve but also to develop therapeutic approaches.

The results of varying the extracellular Na^+ concentration on APs and their repolarization durations are given in Figure **4**. Variation of the extracellular sodium concentration is called as condition 1. The tested concentrations are 125, 142, and 160 mM and for these concentrations maximum depolarizations were 60.95 mV, 63.55 mV and 65.17 mV, resting membrane potentials are -63.04 mV, -60.92 mV and -58.82 mV, and time to peak values are 3.62 ms, 3.12 ms and 2.86 ms respectively.

The results of AP repolarization phases are summarized in the Figure **4B**. APD is not only an indicator of the APD, but also an effective tool to understand the underlying currents of the repolarization phase. Our measurements have shown that the APD period is inversely proportional to the extracellular sodium concentration.

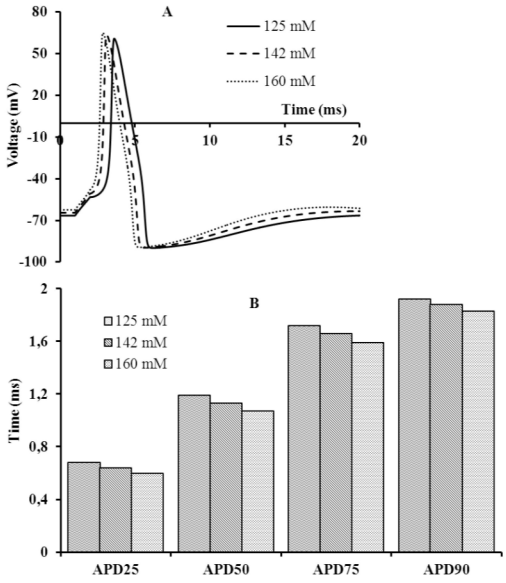

Figure 4: For condition 1 AP and repolarization phase parameters. In **A** APs of varying extracellular sodium concentration from 125 to 160 mM, and in **B** APD at 25% (APD25), 50% (APD50), 75% (APD75) and 90% (APD90) repolarization are given.

The characteristics of simulated APs are given in Figure **5**. Measurements of AP showed that the increase of the extracellular sodium concentration result in a decrease in time to peak values (Figure **5A**). Conversely, maximum depolarization increases systematically with the increase in the extracellular sodium concentration (Figure **5B**). Furthermore, the increase of extracellular sodium depolarizes resting membrane potential (Figure **5C**).

In the light of these results, the extracellular sodium concentration has an extreme importance, especially in the excitability of the nerve cells. The increase of the extracellular sodium causes an easier excitation which means simply the formation of an AP possible with a lower stimulus. Formation of an AP can be called as a bit of information in a binary system which works as a decision mechanism, highly depends on extracellular sodium concentration.

To understand the underlying ionic mechanism under the distinct effect of extracellular sodium concentration on AP parameters, current measurements of the simulations is given in Figure **6**. The effect of systematic increase of extracellular sodium on the sodium currents is given in Figure **6A**. The increase results in an increase in maximum current values. The fitting of activation and inactivation periods showed no difference. Under this condition simulated potassium currents are summarized in Figure **6B**.

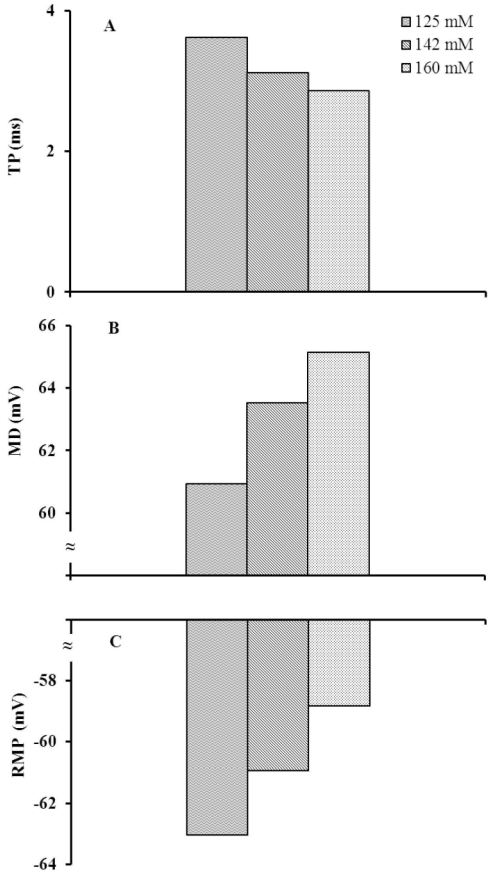

Figure 5: AP parameters of condition 1. In **A** time to peak (TP), in **B** maximum depolarization (MD), in C resting membrane potential (RMP)are given.

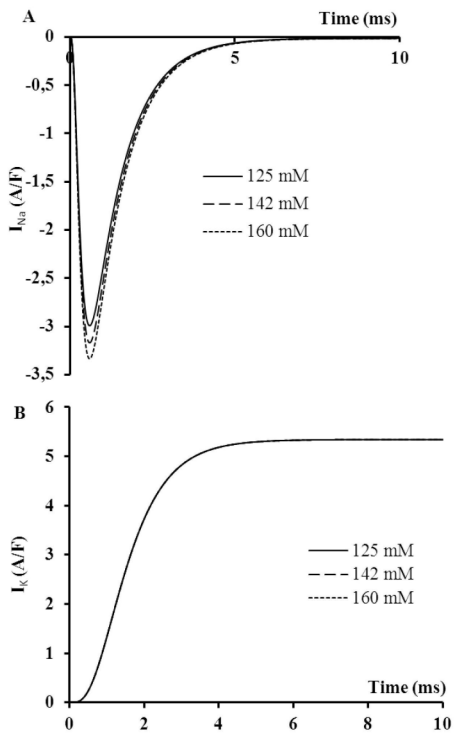

Figure 6: Currents of condition 1. In **A** sodium current density, in **B** potassium current density are given.

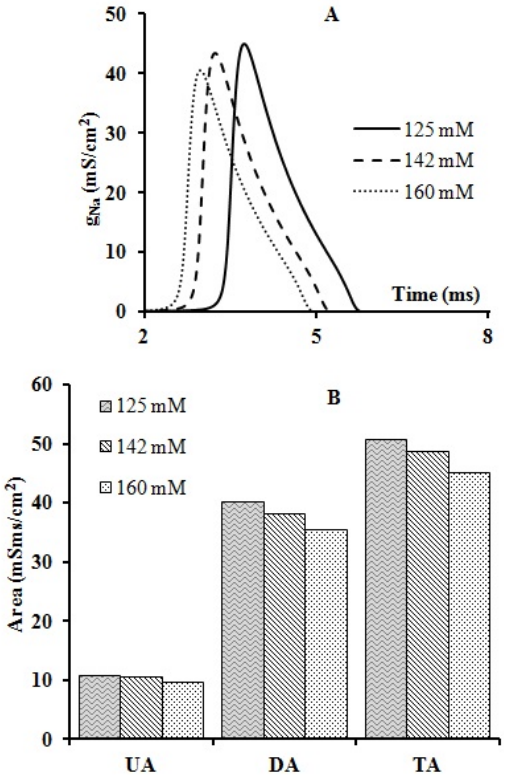

Figure 7: Sodium channel conductivities of condition 1. In **A** conductivity (g_{Na}) of sodium channels, in **B** area under the up phase (UA), area under the down phase (DA), and total area under the conductivity curve (TA) are given.

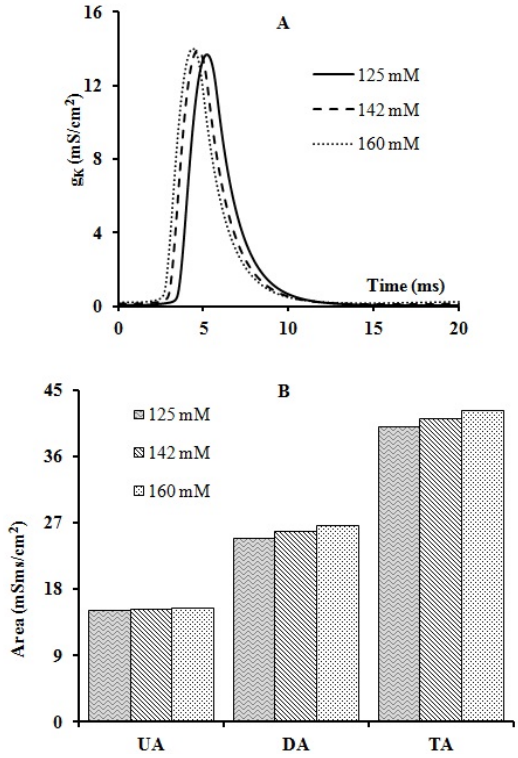

Figure 8: Potassium channel conductivities of condition 1. In **A** conductivity (g_K) of potassium channel, in **B** area under the up phase (UA), area under the down phase (DA), and total area under the conductivity curve (TA) are given for condition 1.

Varying the extracellular sodium concentration has no effect on the potassium currents.

Under the experimental condition 1, sodium conductivities are given in Figure **7** and potassium's are in Figure **8**. For sodium, the increase in extracellular sodium results in not only an increase in conductivity but also a left shift on the time axis (Figure **7**). In accordance with the current recordings increase in sodium concentration more effective on the sodium conductivity.

Our results about the APs and APD values on variant of extracellular potassium concentration so called condition 2 are given in Figure **9**. At first glance K^+ concentration increase results in a shift of AP curves to the left in the time scale. Moreover, repolarization phases of AP decreased for increased concentrations of the extracellular K^+ concentrations (Figure **9B**).

The results of AP parameters are summarized in Figure **10**. Concentration increase results in a decrease in the time to peak values (Figure **10A**), a decrease - critical in 6 mM- in maximum depolarization

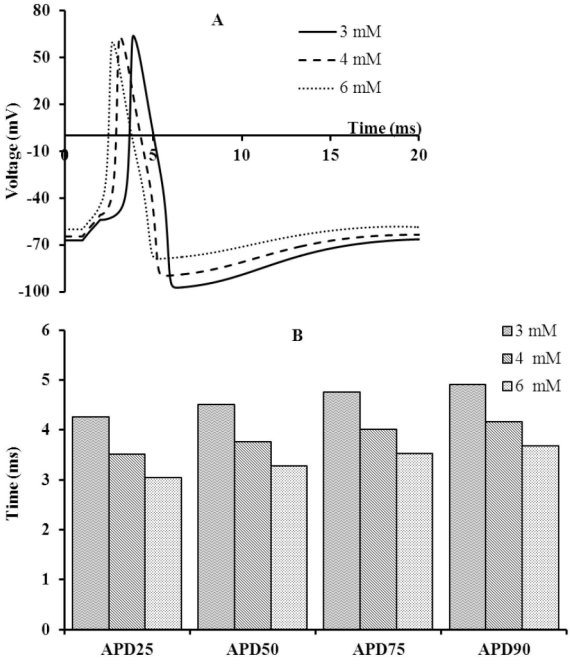

Figure 9: For condition 2 AP and repolarization phase parameters. In **A** APs of varying extracellular potassium concentration from 3 to 6 mM, and in **B** APD at 25% (APD25), 50% (APD50), 75% (APD75) and 90% (APD90) repolarization are given.

(Figure **10B**) and a decrease in resting membrane potential which means depolarization (Figure **10C**).

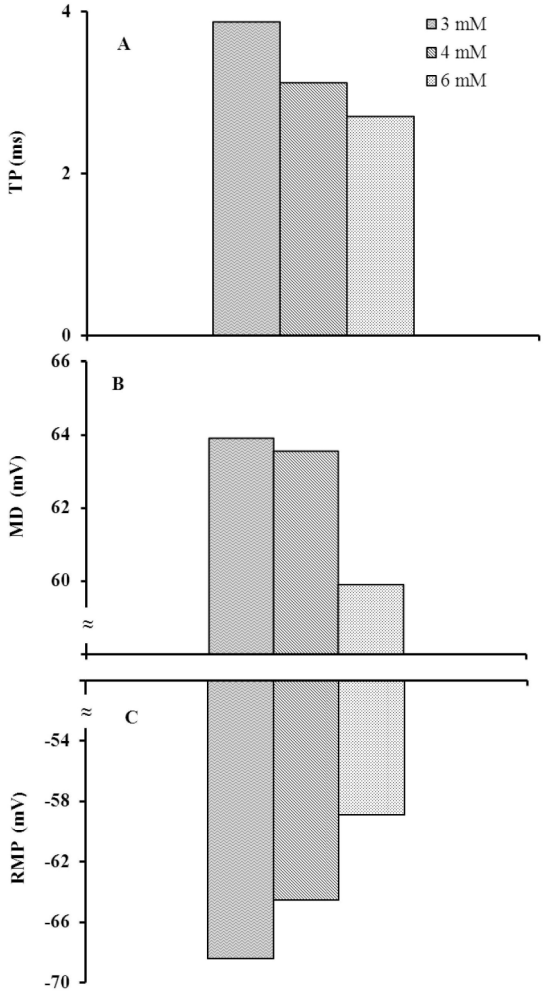

Figure 10: AP parameters of condition 2. In A time to peak (TP), in B maximum depolarization (MD), in **C** resting membrane potential (RMP) are given.

Ionic current results are summarized in Figure **11**. No effect was seen on sodium current but maximum potassium current values were found to be decreased with the concentration increase.

Conductivities for condition 2 are given in Figure **12** and **13** for sodium and potassium ion channels respectively. It is observed that sodium channel conductivity shifts to the left in time axis (Figure **12A**). Area measurement results in a decrease in area with an increase in the extracellular potassium concentration (Figure **12B**). Similar to sodium, potassium channel conductivity shifts to the left in time axis (Figure **13A**). Measured areas were found to be directly proportional to the changes in the concentration (Figure **13B**).

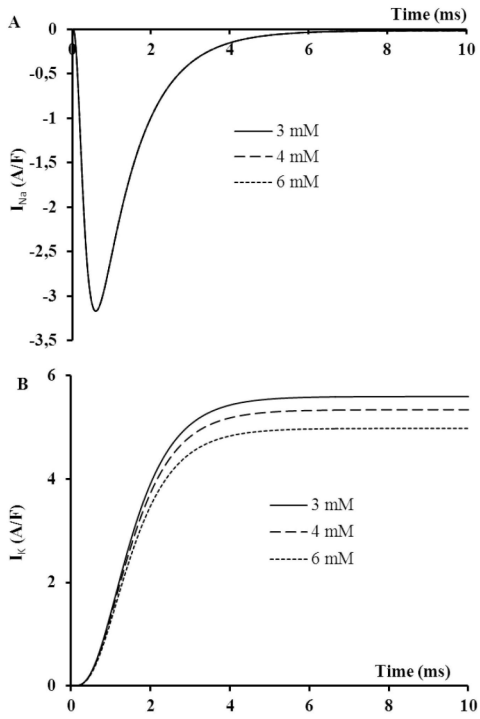

Figure 11: Currents of condition 2. A sodium current, in **B** potassium current densities are given.

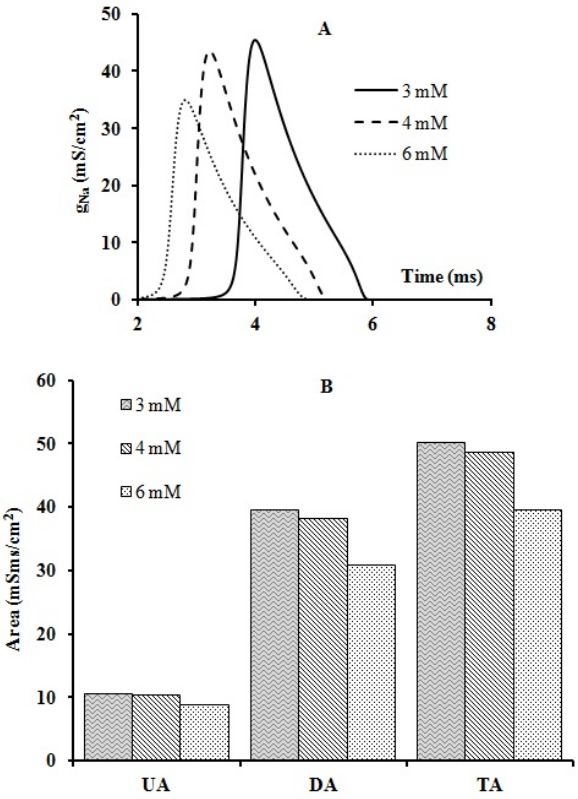

Figure 12: Sodium channel conductivities of condition 2. A conductivity (g_{Na}) of sodium channels, in **B** area under the up phase (UA), area under the down phase (DA), and total area under the conductivity curve (TA) are given.

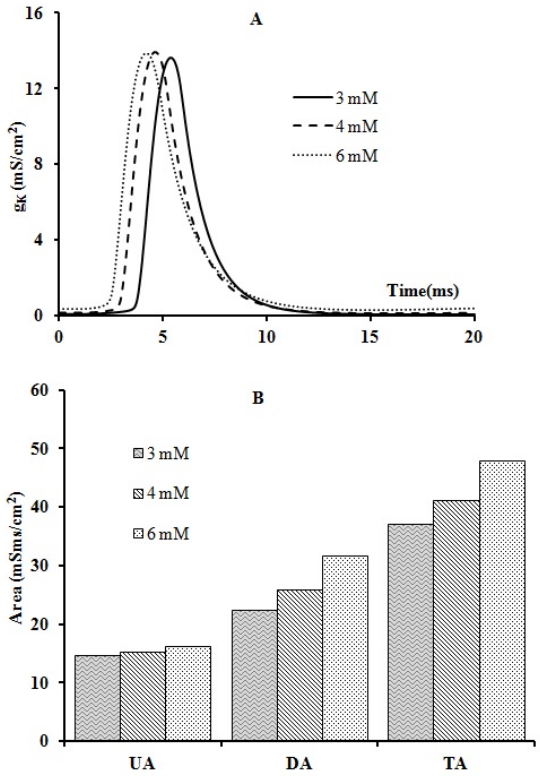

Figure 13: Potassium channel conductivities of condition 2. In **A** conductivity (g_K) of potassium channel, in **B** area under the up phase (UA), area under the down phase (DA), and total area under the conductivity curve (TA) are given for condition 2.

DISCUSSION

Humankind has been doing experiments directly on the systems and/or on the models to explore the universe, to take an advantage of the nature, and to live securely. A model helps us to understand the unknown mechanisms and to test hypothesis thus it is frequently used in many areas. Increased in the tendency to non-linear dynamics has elucidated the tendency of excitable systems (cardiac tissue, nerve cells, and networks of neurons) to exhibit oscillatory, burst, and wave-like phenomena.

Hyponatremia and Hypernatremia (Condition 1)

Sodium ion mostly located in blood and in the fluid around cells. It helps the body keep fluids in a normal balance (osmotic pressure) around the cells. Moreover it also plays a key role in normal nerve and muscle conduction facilities [12].

The body obtains sodium through nutrition and loses it primarily in sweat and urine. Healthy kidneys maintain a consistent level of sodium in the body by adjusting the amount excreted in the urine. When sodium gain and loss are not in balance, the total amount of sodium in the body is affected. The concentration of sodium in the blood may be too low (Hyponatremia) or too high (Hypernatremia) [13].

The body coordinately controls the blood volume and sodium (and other electrolyte) concentrations. When either becomes too high, sensors in the heart, blood vessels, and kidneys detect the increases and stimulate the kidneys to increase sodium excretion. When blood volume or sodium concentration becomes too low, the sensors trigger mechanisms in favor to increasing blood volume.

Some situations (decreased thirst, changes in the kidneys, less fluid in the body, inability to obtain water and drugs) such as fluid loss and/or not enough intake fluid can result in a high sodium level in blood (hypernatremia) and/or dehydration. Since these situations are more common among older people, hypernatremia is also more common among them.

Hypernatremia is poorly tolerated by older people and can result in confusion, coma, and death in its extreme cases. Excess fluid and sodium also occur more commonly in older people because the disorders that usually result in excess fluid (fluid overload)-heart failure, liver disorders, and kidney disease-are also more common in older people [14].

A low sodium level in blood (hyponatremia) is also more common among older people. Hyponatremia usually results when the body retains too much fluid, as occurs in heart failure or liver disease. Hyponatremia also occurs in older people who take certain types of diuretics (thiazide diuretics such as hydrochloro-thiazide), particularly if the kidneys are not functioning regularly. Using liquid nutritional supplements or receiving intravenous fluids that are low in sodium while in the hospital also may cause hyponatremia in older people [14].

Our results on the electrophysiology of the single nerve fiber have shown that under hyponatremic conditions all the measured repolarization times were found to be prolonged. Furthermore simulated single nerve fiber AP's time to peak and resting membrane potentials increased and maximum depolarization points were found to be decreased. This list of changes can be explained by the rundown of the measured sodium currents. Indeed the modification seen in the conductivity of the sodium currents especially in the inactivation phase may be the main cause of all changes. Under hypernatremic conditions however, all

modifications seen were just the reverse of the ones seen under hyponatremic conditions. The only exception seen is the degree of severity on the sodium conductivity which is in parallel with the literature during hyponatremic conditions for conduction velocity [10] and/or oxidative stress [15].

Hypokalemia and Hyperkalemia (Condition 2)

Most of the body's potassium is located inside the cells. It is actually second major ion for the survival of the excitable cells. The body must maintain the potassium level in blood within a fine range. When a potassium level that is too high (Hyperkalemia) or too low (Hypokalemia) it can have serious consequences, such as abnormal heart rhythm in its worst cases, cardiac arrest [16]. The body prefers the potassium to be stored within cells to help the fine tuning of potassium level in blood stream.

The body maintains the right level of potassium by matching the amount of potassium gained with the amount to be lost. Like the sodium it is again gained through nutrition that contains electrolytes and lost primarily in urine. Some potassium is also lost through the digestive tract and in sweat. Healthy kidneys can adjust the excretion of potassium to match the changes in the potassium levels [17].

Typically, the potassium level becomes low if too much is lost from the digestive tract. Sometimes too much potassium is excreted in urine, usually because of drugs that cause the kidneys to excrete excess sodium, water, and potassium (diuretics). In many adrenal disorders, such as Cushing syndrome, the adrenal glands produce too much aldosterone, a hormone that causes the kidneys to excrete large amounts of potassium [18]. Certain drugs cause more potassium to move from blood into cells and can result in hypokalemia. However, these drugs usually cause temporary hypokalemia, unless another condition is also causing potassium to be lost. Hypokalemia is rarely caused by consuming too little potassium because many foods contain potassium.

A slight decrease in the potassium level in blood usually causes no symptoms. A larger decrease can cause muscle weakness, cramping, twitches, and even paralysis. Abnormal heart rhythms may develop.

A high potassium level has many causes, including kidney disorders, drugs that affect kidney function, and consumption of too much supplemental potassium. Usually, hyperkalemia must be severe before it causes symptoms, mainly abnormal heart rhythms. Mild hyperkalemia causes few, if any, symptoms. Sometimes, people may develop muscle weakness. When hyperkalemia becomes more severe, it can cause abnormal heart rhythms. If the level is very high, the heart can stop beating [19].

Under hypo/hyperkalemic conditions our simulation results have shown that the severity of the modification on the AP much more significant compared to hypo/hypernatremic conditions.

Following to hypokalemia all of the measured repolarization phases of AP prolonged significantly. Moreover time to peak, the resting membrane potential and maximum depolarization values were also found to be increased. In parallel to increase in the repolarization phases potassium currents were found to be increased. Interestingly, not only the potassium channel conductivity but also sodium channel conductivity has found to be effected from this conduction. In agreement with the current literature extracellular potassium concentration restriction is important, if not results in many problems such as nerve dysfunction or paralysis [20,21].

CONCLUSIONS AND REMARKS

Like an electrical wire, neurons were recognized to convey information from one part of the body to another in the form of electricity. The process of information transmission accompanies by so called AP very much dependent on the ions around their membranes due to their electrical in nature. As in the case of all electrical messages of the nervous system, the AP is a membrane potential change caused by the flow of ions through ionic channels in the membrane. In our cases our simulation results have shown that sodium ion channel conductivity is much more susceptible to the changes in the extracellular ion concentrations. Our results indicate that the sodium channels are more proned to the changes in the extracellular ion changes than potassium channels. The exact molecular mechanism of this mainly sodium channel centered alterations -especially seen in less tolerated and /or elderly people- needs further investigations.

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