Abstract—We present a simple dynamical model for the transmembrane potential in non-excitable mammalian cells. This model allows us to mimic the effect of nanoparticles on the transmembrane potential, by decreasing the permeability of potassium ion channels. We show that our model agrees with the trends observed in our experiments. However, it also exhibits opposing trends under certain conditions, which were not seen in the experiments. This indicates that the membrane potential can be bistable. We analyze the cellular conditions which may cause this apparent bistability. The effects of adding nanoparticles on sodium and chloride ion channels are also studied using the proposed model. We hypothesize that nanoparticles may also block the sodium and chloride ion channels but the extent of blockage of these ion channels may differ from that of potassium ion channels.

I. INTRODUCTION

All mammalian cells develop a potential difference across their membranes, commonly referred to as the membrane potential or transmembrane potential. The cell membrane allows transport of ions across it through ion channels and ion pumps. However, it is selectively permeable, that is, it has ion channels that selectively allow certain ions to pass through the membrane. This selectivity develops ion concentration gradients across the membrane, which eventually cause a charge build up, and the associated potential difference [1]. At the resting membrane potential, the diffusion forces driving the ions down the concentration gradient balance out the electrical forces due to the potential difference, zeroing the net movement of ions across the membrane. While defining the membrane potential for a cell, the extracellular potential is usually considered the reference. Since the potential inside the cell is lesser compared to that outside, the resting membrane potential for a cell is usually negative. Under normal resting conditions, a cell is referred to as “polarized”. A cell with resting membrane potential closer to zero is considered “depolarized”, while a cell resting at a more negative membrane potential than the normal membrane potential is referred to as “hyperpolarized”.

Cells are categorized as either excitable or non-excitable. A cell falls under the excitable category if it has the capability to generate an action potential. An action potential is a brief event in which the membrane potential first rapidly increases and then rapidly decreases back to its resting state [1]. Cancer cells, and other proliferating cells, are non-excitable in nature. Changes in the transmembrane potential have shown direct correlation with alteration in cell proliferation [2]. This correlation may be used to cure certain diseases, including cancer, which spread due to rapid cell proliferation. There is evidence showing an increase in growth of cancer cells with increased cell depolarization [3]. This motivates us to model the transmembrane potential in non-excitable cells such that it allows us to control the transmembrane potential. It should be noted here that most of the available literature, also discussed later in this section, is on modeling excitable cells. However, studies have shown non-excitable cells to be similar to excitable cells in terms of ionic concentrations with some difference in relative permeability of ions [9], [10], [11]. Hence, we can generalize certain aspects of these models to non-excitable cells as well.

Over the past century, many models have been proposed for the cell membrane potential. Hodgkin and Huxley [4] were the first to analyze the presence of potassium and sodium ionic currents in giant squid axons and presented an electric circuit to model the transmembrane potential and currents. The Hodgkin-Huxley model formed the basis of many more conductance-based models to follow. Connor and Stevens [5] extended this model by adding another transient potassium current to model gastropod neuron somas. Morris-Lecar [6] also presented another extended version of the Hodgkin-Huxley model for barnacle muscle fiber cells. Models for the transmembrane potential are still being proposed to better capture the dynamics of the biological system. Recently, a very useful, but complex model in [7] presented a system of differential equations to relate transmembrane potentials, ionic concentrations and cell volume of cells. Another very recent model was presented in [8] pointing out the possibility of having a bistable behavior in non-excitable cells similar to that seen in excitable cells. However, all the models mentioned above are either too complex for analysis or lack the ability to control the membrane potential through an external stimulus.

Transmembrane potential, like many other biological processes, exhibits nonlinear dynamics [12]. Examples can be
found on simulating such nonlinear biological processes [13]. Simulating the dynamics can allow better understanding of the underlying biological process [14]. Moreover, there is evidence that addition of nanoparticles in the vicinity of the cell, affects the membrane potential by blocking certain ion channels [15]. In our work, we sought to develop a nonlinear model for the transmembrane potential which is accessible to control-oriented analysis, with the control input being the addition of nanoparticles. We take inspiration from the fact that if we can control the transmembrane potential, we can control the proliferation of cancer cells and hence provide a possible cure for the disease in the future.

The aim of this paper is to come up with a simple dynamic model which allows controlling of the resting transmembrane potential of cell by regulating the permeability of its ion channels. Our model is shown to be stable over a wide range of permeability values and is seen to agree with the experimental values of resting membrane potential if certain constraints are met. The model successfully predicts the effect on membrane potential of adding nanoparticles in the vicinity of the cell. This paper provides an improvement to our earlier presented model in [16] by overcoming certain limitations mentioned later. We also show that our model exhibits a different behavior under certain set of constraints, which agrees with the work in [8]. The proposed model can also be used to study the transient behavior of transmembrane potential. Apart from that, we point out that using another set of equations mentioned in [17] leads to a model with unstable transmembrane potential.

This paper is organized in the following manner. In section II, we present the experimental results that motivate this work. Section III provides the background on existing cellular models. We present our proposed model for controlling transmembrane potential in Section IV. In Section V, we analyze the stability of the equilibrium points of the proposed model. We present the apparent bistability of the membrane potential, back our hypothesis with simulation results and compare them with experimental data in section VI. In Section VII, we further analyze our proposed model to see the possible effect of nanoparticles on the ion channels not observed in experiments. Section VIII presents the conclusion and ideas for future work.

II. EXPERIMENTAL RESULTS

Experimental data was collected for two cell species: CHO (Chinese Hamster Ovary) cells and HeLa (human cervical cancer) cells. Both these cells are of the non-excitabile and proliferating kind and are widely used for experimentation purposes. To set up the experiment, the cytosol of the cells were stained with green-fluorescent DiBAC₄(3) (bis-(1,3-dibutyl)barbituric acid) trimethine oxonol). DiBAC₄ is known to diffuse more into the cell on increased depolarization, hence we expect an increase in the DiBAC fluorescence when the cell depolarizes. The cells were treated with different concentrations of 60nm amine-modified polystyrene nanoparticles and the DIBAC fluorescence was monitored using flow cytometry and fluorescence microscopy. Details on the experimental setup and the results are provided in [15]. Figure 1 shows the CHO cells without and with the incubation of nanoparticles. The red-fluorescent nanoparticles bind to the exterior of the cell membrane. An increase in the green fluorescence of DIBAC is visible in the cells treated with nanoparticles. Similar trends were observed for HeLa cells.

It was concluded in the experiments that the introduction of nanoparticles causes cells to depolarize. On further investigation, it was also found that nanoparticles directly affect the permeability of potassium ion channels by blocking the channels. This causes an accumulation of positive charge inside the cell, hence causing depolarization [15].

In the sections to follow, we create a model to fit these experimental results. The next section provides the foundational models which we extend to build up our model.

III. BACKGROUND

Figure 2 shows a simplified representation of a model cell under normal conditions as described in [17]. The ion channels are shown to be passages through the cell membrane that allow passive movement of three types of ions to and from the cell, that is, $Cl^-$ (chloride), $Na^+$ (sodium) and $K^+$ (potassium). These channels are characterized by their relative permeability, that is, the relative ease with which the ions can flow through them. The resting membrane potential is $V_{mr} = -80mV$ for the ionic concentrations mentioned in the figure and relative permeability $P_K = 1.0, P_{Na} = 0.02, P_{Cl} = 2.0$. The figure also shows the channels being blocked by nanoparticles, depicted as red circles.

A. Hodgkin-Huxley Model

In order to model the electrical activity in cell membrane, Hodgkin and Huxley [4] presented a basic electrical circuit appropriate to model a giant squid axon as shown in Fig. 3. In this model, the membrane is represented by a capacitor with capacitance $C_m$, called the transmembrane capacitance. Also in the model, there is a sodium conductance $G_{Na}$, a potassium conductance $G_K$ and a chloride or leakage conductance $G_{Cl}$. The values of these conductances depend on the relative permeability of each individual ion channel. A channel with higher permeability will have a higher value...
of conductance. The membrane potential $V_m$ is considered to be the potential inside the cell minus the potential outside the cell and all the individual channel currents $I_K$, $I_{Na}$ and $I_{Cl}$ are positive in the outward direction (leaving the cell). The individual potentials generated by each ion species are represented by batteries ($E_K, E_{Na}, E_{Cl}$). There is also an externally applied current in the model represented by $I_{ext}$. Although this model was developed for a particular type of excitable cells, the giant squid axon, it has been extended to be the potential inside the cell minus the potential outside externally applied current in the model represented by $I_e$. Let’s further analyze this electrical circuit.

Applying the Kirchoff’s Current Law to the circuit in Figure 3 gives,

$$I_K + I_{Na} + I_{Cl} = I_{ext} - C_m \dot{V}_m$$

\[ (1) \]

The ion channels mentioned earlier are passive channels, that is, they do not require an energy source for the transport of ions. They facilitate the movement of ions down their concentration gradients. Cells also contain active channels which make use of energy sources by sources like ATP (adenosine triphosphate) to drive ions. One such active channel is the sodium-potassium pump. This ion pump, shown in Figure 2, exports three $Na^+$ ions in exchange for two $K^+$ ions in every cycle of operation.

Adding a term for pump current and also setting $I_{ext} = 0$ since we are not applying any external current,

$$I_K + I_{Na} + I_{Cl} + I_{pump} = -C_m \dot{V}_m$$

\[ (2) \]

This equation needs to be satisfied by the currents and the transmembrane potential at all times.

**B. Ion Channel Currents**

We make use of the energy barrier model (3a) proposed in [17] to represent the various ionic currents in units of $\mu A$ (microamperes). The pump current model is also taken from [17]. The currents are represented by the following set of equations,

$$\psi(t) = \frac{z}{RT} F V_m(t)$$

\[ (3) \]

$$I_K(\psi(t)) = \frac{P_K}{z} F z_K ([K^+]_i e^{\psi(t)} - [K^+]_o)$$

\[ (4) \]

$$I_{Na}(\psi(t)) = \frac{P_{Na}}{z} F z_{Na} ([Na^+]_i e^{\psi(t)} - [Na^+]_o)$$

\[ (5) \]

$$I_{Cl}(\psi(t)) = \frac{P_{Cl}}{z} F z_{Cl} ([Cl^-]_i e^{\psi(t)} - [Cl^-]_o)$$

\[ (6) \]

$$I_{pump}(t) = \frac{\beta - 1}{\beta} \cdot \frac{2.17 [ATP]^z}{(1 + [Na^+]_o)^{3/5}}$$

\[ (7) \]

where,

$P_X (cm^2 s^{-1})$ - the relative permeability of ion channel X, $F (C mol^{-1})$ - the Faraday’s constant, $z_X$ - the number of valence electrons, $z_K = z_{Na} = z_{Cl} = 1$, $R (J mol^{-1} K^{-1})$ - the gas constant, $T(K)$ - the absolute temperature, $\beta$ - the pump ratio, $[ATP](mM)$ - the concentration of ATP (time-dependent), $[X]_i(mM)$ - the intracellular concentration of ion X, $[X]_o(mM)$ - the extracellular concentration of ion X, $[X]_c(mM)$ - the half-maximal occupation concentration.

**IV. THE PROPOSED MODEL**

We can simplify our set of equations by introducing the permeability factors, $\alpha_1 = P_K F z_K$, $\alpha_2 = P_{Na} F z_{Na}$ and $\alpha_3 = P_{Cl} F z_{Cl}$. Also let’s make the substitution $k = \frac{F}{RT}$. Note that all these parameters are non-negative and bounded. Equations (4), (5), (6) can now be re-written as follows,

$$I_K(V_m(t)) = \alpha_1 ([K^+]_i e^{kV_m(t)} - [K^+]_o)$$

\[ (8) \]

$$I_{Na}(V_m(t)) = \alpha_2 ([Na^+]_i e^{kV_m(t)} - [Na^+]_o)$$

\[ (9) \]

$$I_{Cl}(V_m(t)) = \alpha_3 ([Cl^-]_i e^{kV_m(t)} - [Cl^-]_o)$$

\[ (10) \]

Substituting the current equation (8), (9) and (10) in equation (2) gives the following,

$$-\dot{V}_m(t) = \frac{k V_m(t)}{C_m} (\alpha_1 [K^+]_i + \alpha_2 [Na^+]_i + \alpha_3 [Cl^-]_o)$$

\[ (11) \]

$$-\dot{V}_m(t) = \frac{1}{C_m} (\alpha_1 [K^+]_o + \alpha_2 [Na^+]_o + \alpha_3 [Cl^-]_i)$$

\[ (11) \]

$$+ \frac{1}{C_m} I_{pump}(t)$$

Let’s analyze the individual terms in the above equation. Since it is known that the nanoparticles effect the potassium channel permeability, we consider $\alpha_1$ to be the controllable parameter. The other permeability factors $\alpha_2$ and $\alpha_3$ may also be effected, but since we do not have experimental evidence to justify this, we consider them fixed in our model.
model. In order to maintain normal operating conditions, a cell maintains the intracellular concentrations \([K^+]_i\), \([Na^+]_i\) and \([Cl^-]_i\). The extracellular concentrations \([K^+]_o\), \([Na^+]_o\) and \([Cl^-]_o\), can also be considered constant or slowly varying compared to the dynamic changes in transmembrane potential. Ion channel currents arise in order to keep these ionic concentrations constant. Moreover, in order to maintain stable chemical concentrations in the cell, the ion pump current \(I_{pump}\) has to have a relatively steady value as well. Hence, we can introduce the following constants,

\[
a = \frac{1}{C_m}[K^+]_i, \quad b = \frac{1}{C_m}[K^+]_o, \quad c = \frac{1}{C_m}(\alpha_2[Na^+]_i + \alpha_3[Cl^-]_o) \quad \text{and} \quad d = \frac{1}{C_m}(\alpha_2[Na^+]_o + \alpha_3[Cl^-]_i - I_{pump})
\]

The model in (11) now becomes,

\[
V_m(t) = -(\alpha_1 a + c)e^{kV_m(t)} + \alpha_1 b + d
\]

Considering the state variable \(z(t) = e^{kV_m(t)}\), with the time derivative \(\dot{z}(t) = kz(t)V_m(t)\) and substituting equation (16),

\[
\dot{z} = kz(-\alpha_1 a + c)z + \alpha_1 b + d
\]

V. Stability Analysis

The system in Equation (17) has two isolated equilibrium points, \(z_{01} = 0\) and

\[
z_{02} = \frac{\alpha_1 b + d}{\alpha_1 a + c}
\]

The equilibrium point \(z_{01}\) however leads to a resting membrane potential \(V_{mr} = -\infty\) which is not possible in reality. Therefore we disregard this equilibrium point. For the other equilibrium point \(z_{02}\) we can reformulate the system around this equilibrium point as,

\[
\dot{z} = -kz(\alpha_1 a + c)(z - z_{02})
\]

To analyze the stability of the system in (19) around this equilibrium point, let’s consider the Lyapunov function [18] \(V = \frac{1}{2}(z - z_{02})^2\), the time derivative of which gives \(\dot{V} = -kz(\alpha_1 a + c)(z - z_{02})^2\). Since \(a, c > 0\) and \(\alpha_1 \geq 0\) for cells under normal conditions and \(z = e^{kV_m} > 0\), we notice that \(\dot{V} < 0\) for all \(z \in \mathbb{R}_+\) and \(\dot{V} = 0\) for \(z = z_{02}\). Hence, the equilibrium at \(z = z_{02}\) is asymptotically stable.

Since \(z_{02} = e^{kV_{mr}}\), the corresponding resting membrane potential is,

\[
V_{mr} = \frac{1}{k} \ln \left(\frac{\alpha_1 b + d}{\alpha_1 a + c}\right)
\]

Equation (20) becomes equivalent to the well-known Goldman-Hodgkin Katz (GHK) equation for the resting membrane potential [19] if we substitute (12), (13), (14) and (15) back in (20) and remove the pump current term \(I_{pump}\). Although \(I_{pump}\) is not available for control, its contribution to the membrane potential becomes negligibly small when the denominator in (20) is large enough, which is the case under normal operating conditions. Hence, we can expect the resting membrane potential obtained from this model not to deviate much from the GHK equation for relatively large values of the permeability factors \(\alpha_1\), \(\alpha_2\) and \(\alpha_3\). For lower values of the permeability factors however, the pump current has important implications on the system. This will be shown in the section to follow.

It should also be noted here that using the ionic current model (3b) from [17] instead of (3a), results in a system with an unstable equilibrium point. This does not agree with reality since the cell membrane potential always rests at a particular value. It is also important to note that the membrane potential equation (8) in our previous work [16] disagrees with the Hodgkin-Huxley model and also the resting membrane potential provided by the associated model disagrees with the GHK equation. Our new model manages to overcome these limitations.

VI. Bistability and Simulation Results

As evident from the expression in (18), the equilibrium point \(z_{02}\) and the corresponding resting membrane potential \(V_{mr}\) are dependent on the potassium permeability factor, \(\alpha_1\). However, the variation in \(z_{02}\) with respect to \(\alpha_1\) exhibits two opposing trends under different cellular conditions. The cellular conditions here refer to the permeability factors of the ion channels other than the potassium ion channel. For the purpose of analysis, we assume that we have the capability to set these permeability factors as desired. In this section, we first provide the set of conditions which characterize the two opposing scenarios and then we go on to present them in simulation. We conclude this section by comparing the simulation results with the experimental data.

A. Bistability of the Membrane Potential

Let’s consider dependence of \(z_{02}\) on \(\alpha_1\),

\[
\frac{\partial z_{02}}{\partial \alpha_1} = \frac{bc - ad}{(\alpha_1 a + c)^2}
\]

We see that the expression in (21) is negative if \(ad > bc\), causing an increase in \(z_{02}\) and hence depolarization if \(\alpha_3\) is decreased. However, if \(ad < bc\), a decrease in \(\alpha_1\) would rather cause hyperpolarization.

B. Simulation Results

The two cases mentioned in the previous subsection can be achieved by setting the permeability factors \(\alpha_2\) and \(\alpha_3\) to two different sets of desired values. This means we choose \(c \text{ and } d\) in (21) to have certain constant values. However, the parameters \(a\) and \(b\) are independent of \(\alpha_2\) and \(\alpha_3\) and hence cannot be set as desired. Fixing \(\alpha_2\) and \(\alpha_3\), we vary \(\alpha_1\) over a range of values. A decrease in \(\alpha_1\) can be interpreted as adding more nanoparticles to the cell. We simulate the effect of these variations on the state variable \(z(t)\) and the membrane potential \(V_m(t)\).

We use the parameters, \(T = 295.15 K\), \(R = 8.314 JK^{-1}mol^{-1}\) and \(F = 96485 Cmol^{-1}\). The values of pump current \(I_{pump} = 15 pA\) and membrane capacitance \(C_m = 37 pF\) have been chosen in accordance with the measurements provided in [20]. The external and internal
IONIC CONCENTRATIONS ARE TAKEN TO BE THE ONES PROVIDED IN [17], ALSO MENTIONED ON FIGURE 2.

TO SIMULATE THE FIRST SCENARIO, WE CHOOSE $\alpha_2 = 2 \times 10^{-7}$ AND $\alpha_3 = 2 \times 10^{-5}$ SUCH THAT $ad > bc$, AND SMOOTHLY VARY $\alpha_1$ IN THE INTERVAL $[5 \times 10^{-7}, 5 \times 10^{-4}]$. FIGURE 4A SHOWS HOW THE EQUILIBRIUM POINT $z_{02}$ VARIES WITH INCREASE IN $\alpha_1$. WE NOTICE THAT AS $\alpha_1$ BECOMES SMALL, $z_{02}$ INCREASES, EVENTUALLY APPROACHING $\frac{9}{2} = 0.0513$. ALSO, SINCE $V_{mr} = \frac{1}{2} \log(z_{02})$, $V_{mr}$ INCREASES TO $-0.076V$ AS $\alpha_1$ DECREASES AS SHOWN IN FIGURE 4B. TO SIMULATE THE TRANSIENTS OF $z(t)$ AND $V_m(t)$, WE EVOLVE THE TWO VARIABLES WITH TIME AS SHOWN IN FIGURES 4C AND 4D RESPECTIVELY FOR A GIVEN $\alpha_1$. THE RED-SOLID CURVE CORRESPONDS TO $\alpha_1=2 \times 10^{-7}$, THE BLUE-DASHED CURVE REPRESENTS $\alpha_1=1 \times 10^{-6}$, WHILE THE BLACK DASH-DOTTED CURVE IS FOR $\alpha_1=2 \times 10^{-6}$. OBSERVING THE PLOTS REVEALS THAT $z$ AND $V_m$ COME TO REST AT HIGHER VALUES (DEPOLARIZED) IF $\alpha_1$ IS DECREASED.

FOR THE OTHER CASE, WE MAKE $ad < bc$ BY SETTING $\alpha_2 = 2 \times 10^{-8}$ AND $\alpha_3 = 2 \times 10^{-6}$. AS IN THE PREVIOUS CASE, $\alpha_1$ IS SMOOTHLY VARIED IN THE INTERVAL $[5 \times 10^{-7}, 5 \times 10^{-4}]$. THE PLOTS IN FIGURE 5A AND FIGURE 5B SHOW THE CORRESPONDING EFFECT ON $z_{02}$ AND $V_{mr}$. THE PLOTS FOR THE TRAJECTORIES OF $V_m(t)$ AND $z(t)$ FOR $\alpha_1=2 \times 10^{-7}$ (RED-SOLID CURVE), $\alpha_1=1 \times 10^{-6}$ (BLUE-DASHED CURVE), $\alpha_1=2 \times 10^{-6}$ (BLACK DASH-DOTTED CURVE) ARE ALSO PROVIDED IN FIGURE 5D AND 5C. UNLIKE THE PREVIOUS CASE, IT IS OBSERVED THAT DECREASING $\alpha_1$ HYPERPOLARIZES THE CELL RATHER THAN DEPOLARIZING IT.

C. COMPARISON WITH EXPERIMENTAL RESULTS

IN SECTION II, WE PRESENTED EXPERIMENTAL EVIDENCE CONCLUDING THAT THE ADDITION OF NANOPARTICLES CAUSED DEPOLARIZATION OF THE CELLS. FURTHER EXPERIMENTATION IDENTIFIED THE BLOCKING OF POTASSIUM ION CHANNELS BY NANOPARTICLES AS A CAUSE OF THE OBSERVED DEPOLARIZATION.

FROM THE PREVIOUS SUBSECTION, WE SEE THAT OUR SIMULATION RESULTS OF THE PROPOSED MODEL AGREE WITH THE TRENDS SEEN IN THE EXPERIMENTS WHEN $ad > bc$. THE PARAMETER $\alpha_1$ CORRESPONDS TO THE PERMEABILITY OF POTASSIUM ION CHANNELS AND AN ADDITION OF NANOPARTICLES CAUSES IT TO DECREASE. THE SIMULATION RESULTS FOR THIS CASE DEPICT AN INCREASE IN $V_{mr}$ IF $\alpha_1$ IS DECREASED, IN AGREEMENT WITH THE EXPERIMENTAL DATA. ON THE OTHER HAND, IF THE CELLULAR CONDITIONS ARE SUCH THAT $ad < bc$, WE SEE OPPOSITE TRENDS AS COMPARED TO THE EXPERIMENTS.

IN VIEW OF THE PRESENTED SIMULATION RESULTS, WE CONCLUDE THAT THE TRANSMEMBRANE POTENTIAL IS BISTABLE, EXHIBITING EITHER DEPOLARIZATION OR HYPERPOLARIZATION UNDER A DIFFERENT SET OF PERMEABILITY FACTORS. THE HYPERPOLARIZATION STATE, HOWEVER, IS ONLY ACHIEVED WHEN THE PERMEABILITY FACTORS BECOME VERY SMALL. THE WORK PRESENTED IN [8] ALSO INDICATES THE POSSIBILITY OF A SIMILAR BISTABLE BEHAVIOR.

VII. EFFECT ON SODIUM AND CHLORIDE ION CHANNELS

ALTHOUGH EXPERIMENTAL EVIDENCE SUGGESTS THAT NANOPARTICLES BLOCK THE POTASSIUM ION CHANNELS, WE CAN NOT IGNORE THE POSSIBLE EFFECT OF ADDING NANOPARTICLES ON THE SODIUM AND CHLORIDE ION CHANNELS. WE ANALYZE THE EFFECT ON THESE CHANNELS AT THE IONIC CONCENTRATIONS PROVIDED IN [17]. EXPANDING THE EXPRESSION FOR $z_{02}$ IN (18),

$$z_{02} = \frac{5\alpha_1 + 145\alpha_2 + 7\alpha_3 - 15 \times 10^{-12}}{140\alpha_1 + 10\alpha_2 + 150\alpha_3} \tag{22}$$

COMPUTING THE RATE OF CHANGE OF $z_{02}$ WITH RESPECT TO $\alpha_2$ AND $\alpha_3$,

$$\frac{\partial z_{02}}{\partial \alpha_2} = \frac{20250\alpha_1 + 21680\alpha_3 + 15 \times 10^{-11}}{(140\alpha_1 + 10\alpha_2 + 150\alpha_3)^2} \tag{23}$$

$$\frac{\partial z_{02}}{\partial \alpha_3} = \frac{230\alpha_1 - 21680\alpha_2 + 2 \times 10^{-9}}{(140\alpha_1 + 10\alpha_2 + 150\alpha_3)^2} \tag{24}$$

OBSERVING (24), WE SEE THAT AS LONG AS THE RELATION $21680\alpha_2 - 230\alpha_1 > 2 \times 10^{-9}$ IS OBEYED, WE CAN CONSIDER THE DECREASE IN CHLORIDE ION PERMEABILITY $\alpha_3$ AS A POSSIBLE CONTRIBUTOR TO THE DEPOLARIZATION SEEN IN EXPERIMENTS. THIS SUGGESTS THAT $\alpha_2$ MUST NOT BE SMALLER THAN A PARTICULAR LIMIT FOR A GIVEN $\alpha_1$. IN OTHER WORDS, THIS SUGGESTS THAT THE RATE OF DECREASE OF SODIUM ION PERMEABILITY $\alpha_2$ WITH RESPECT TO THE NUMBER OF ADDED NANOPARTICLES, SHOULD EITHER BE DECREASING WITH INCREASING NANOPARTICLES OR SHOULD REMAIN NEGligiably SMALL FOR ANY NUMBER OF NANOPARTICLES.

ON THE OTHER HAND, EXAMINING (23) SUGGESTS THAT $\frac{\partial z_{02}}{\partial \alpha_2}$ IS ALWAYS POSITIVE, NO MATTER WHAT THE VALUES OF THE PERMEABILITY FACTORS.
factors are. Hence, there is no scenario where we can consider the blocking of sodium ion channels by nanoparticles as a sole contributor to the depolarization effect. However it is possible that the decrease in $\alpha_2$ due to addition of nanoparticles is such that the hyperpolarization effect caused by it is always smaller as compared to the depolarization caused by a decrease in $\alpha_1$ and $\alpha_3$ combined under the satisfaction of the constraints mentioned earlier.

In a nutshell, analysis of the effect of individual permeability changes on $2\alpha_2$ and the associated $V_m$, suggests that in order to cause cellular depolarization, nanoparticles may also block chloride ion channels apart from the potassium ion channels. They may also block the sodium ion channels but the effect is not as prominent as the other channels. Currently, we have experimental evidence for the blocking of potassium ion channels only. Further experimentation on the other ion channels will be useful to test our theoretical hypothesis.

VIII. CONCLUSIONS AND FUTURE WORK

In this paper, we presented a simple dynamical system to model the transmembrane potential of biological cells. Our model allows the control of transmembrane potential by manipulating the potassium channel permeability and is shown to be stable as well. Experiments revealed that potassium channel permeability is decreased by the introduction of nanoparticles in the vicinity of the cell, causing depolarization. Hence, decrease in this permeability in simulation can be considered equivalent to adding more nanoparticles into the cell. We simulate our model for a given set of internal and external ionic concentrations and qualitatively compare the simulation trends with the experimental results. Our simulation shows the same depolarization trend for decreasing the potassium channel permeability. However, we also see opposing trends, that is, hyperpolarization of the cell under another set of conditions. This indicates a bistable behavior of the transmembrane potential. Also, theoretical analysis of the proposed model points out the possibility that nanoparticles block the sodium and chloride ion channels as well. However the extent to which the sodium and chloride ion channels are blocked may not be the same as the potassium ion channels. The model presented can be used to fit different types of cells and can enable us to predict the potassium channel permeability required to achieve a desired membrane potential. Nanoparticles can then be introduced into the cell to produce the corresponding desired permeability.

In order to find the amount of nanoparticles that should be added to achieve this desired permeability, we also need to model the dependence of ion channel permeability on the amount of nanoparticles. Moreover, we have to account for the effect of adding nanoparticles on the sodium and chloride ion channels. In the future, we propose to add more states to the system to incorporate these dynamics.

REFERENCES