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Semi Analytic Solution of Hodgkin-Huxley Model by Homotopy Perturbation Method

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Abstract.: Hodgkin-Huxley model is a system of four non-linear coupled differential equations which describes and explains the threshold and action potential by a stimulus arising in a single neuron. The solution and analysis of Hodgkin-Huxley equations is a formidable task because of the coupling between non-linear differential equations, lots of unknowns and their dependence on many physical parameters. Although this model has been solved by numerical methods, finding an analytic solution is interesting due to the challenges that the continuum model offers. In this paper, first order semi analytic solution of this model, in space-clamped situation, is derived by Homotopy Perturbation Method. We applied this technique in piece wise manner due to the strong and complex coupling between the variables in the model. Without this modification, finding an accurate analytic solution is impossible for this neural model. Results show that computed analytic solution has excellent agreement with higher order numerical solution. Robustness of the computed analytic solution in different physical scenarios is examined. Further, this analytic solution can describe many key properties such as the threshold potential, the action potential and the refractory period. MATLAB software is used to simulate the solution.

AMS (MOS) Subject Classification Codes: 34E10 ; 34A25 ; 34A34 ; 34A45 ; 92C20
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1. INTRODUCTION

In the past few decades, extensive research has been dedicated to understand the function of the brain and neural activity, giving rise to many mathematical models and theories that describe the dynamical behavior of neurons (brain cells or nerve cells). One of them is the widely known Hodgkin-Huxley model. In 1952, physiologists Alan Lloyd Hodgkin and Andrew Huxley presented the model on the bases of experimental investigations and theoretical analysis performed on giant squid axon. This model describes the underlying ionic mechanisms in the initiation and propagation of action potentials in neurons. They presented their experimental and theoretical work in a series of five papers [20, 21, 22, 23, 24]. For their work, they were awarded the 1963 Nobel Prize in Physiology and Medicine. Full Hodgkin-Huxley model is a set of four non-linear partial differential equations which describes and explains the threshold and action potential in nerve pulse propagation. The Hodgkin-Huxley model for the so-called space clamped situation is a mathematical model consisting of four nonlinear ordinary differential equations that describes membrane action potentials [35, 36].

Most of the nonlinear differential equations can not be solved exactly, therefore, are often approached through numerical techniques. In the last few decades, semi analytic solution techniques such as Adomian Decomposition Method (ADM) [1], Variation Iteration Method (VIM) [12, 13], Homotopy Analysis Method (HAM) [29, 30] and Homotopy Perturbation Method (HPM) [14] have been employed for solving linear as well as nonlinear differential equations. The technique which is employed in this work is Homotopy Perturbation Method. The homotopy perturbation method merges two techniques, the standard homotopy technique and the perturbation technique. In this method, the solution is computed in the form of an infinite series of functions which converges rapidly to the accurate solution. This method is generally accepted as a robust analytical technique for solving nonlinear differential equations. The method was seminally proposed by Ji-Huan He in 1999 in his work [14], and later, improvised and elaborated upon by him in [15, 16]. This method has successfully led to analytic or approximate analytic solutions of various nonlinear differential equations, and can be abundantly found in the literature. A non-exhaustive list of which may be [17, 18, 19, 31, 7, 26, 11, 4, 5, 27, 28, 33, 6, 10].

The analysis of Hodgkin-Huxley equations is difficult because of the non-linearity and coupling of variables. Even though it has been illustrated by Hearne et al in 1994 that approximate analytic solution of Hodgkin-Huxley equations do exist which they presented in the form of Voltera integrals, so far, actual solutions of the Hodgkin-Huxley equations are computed only through numerical techniques. In this paper, approximate analytic solution of space-clamped Hodgkin-Huxley model is presented in two situations, (1) a brief pulse of current is applied as a stimulus and (2) a constant sustained current is applied as a stimulus. The analytical solution technique as discussed in this paper may pave the way for solving similar models analytically, and the challenge therefore forms the main impetus of this work.

The remaining paper is organized as follows. In Section 2, a brief description about anatomy and physiology of neurons is given. In Section 3, a brief review of Hodgkin-Huxley model is presented. Section 4 consists of description of Homotopy Perturbation Method. In Section 5 approximate analytic solution of Hodgkin-Huxley model is presented

and an algorithm for the calculation of first order approximate analytic solution of the model is given. Moreover, this section includes the convergence proof of one of the series solution. Section 6 consists of results in different situations (1) impulsive current, and (2) constant current; as well as the discussion about the solutions. Furthermore, this section contains the comparison of the analytic results with the accepted numerical results [9]. Section 7 comprises concluding remarks and prospective future work.

2. A BRIEF ANATOMY AND PHYSIOLOGY OF NEURONS

Neuron is the basic structural element of the nervous system. Each neuron consists of soma (or body) and arm-like *processes* called dendrites and axon. An axon is a long process whose function is to convey impulses from the cell body to other nerve cells or to peripheral organs; only one such process extends from the cell body. Dendrites are numerous processes whose function is the reception of impulses arriving from other neurons. The body and processes of a nerve cell are covered with a selectively permeable membrane which is mainly composed of lipid and protein molecules. In the cell membrane, there are small pores or channels, through which molecules of water, ions and other substances pass in and out of the cell [3]. When Hodgkin and Huxley were performing experiments, and evolving their model, there was very limited information about ion channels, but the model that they developed is still valid under the concept of ion channel. Differences in the concentrations of ions on opposite sides of a cellular membrane lead to a voltage called the *membrane potential*. There are electrical potentials in nerve cells both at rest and during excitation. At rest, there is a potential difference, called *resting membrane potential*, of the order of 60-90 millivolts between the outer surface of a nerve cell and its protoplasm, the cell surface being electrically positive with respect to protoplasm. If a sufficient strong stimulus is applied to a neuron, such that the level of depolarization in the cell reaches some critical level, called the *threshold*, it will give rise to excitation and causes a rapid change in the membrane potential, which is known as *action potential*. During the action potential, the polarity of the cell membrane is reversed briefly i.e. the inside of the cell becomes temporarily electrically positive relative to the outside. This depolarizing pulse propagates along the axon of the nerve cell to reach the other cells. If the stimulus is insufficient to produce an action potential, response of the cell is called *sub-threshold response* [3].

Many theories have been developed to explain the underlying mechanism in potentials. Hodgkin, Huxley and Katz performed many experiments and presented a theory of action potential which is widely accepted now. In 1939, Hodgkin and Huxley recorded the first accurate observation of membrane potentials on the axon of the stellar nerve of the squid. This theory suggests that bioelectrical potentials are due to unequal concentrations of potassium (K^+), sodium (Na^+) and chlorine (Cl^-) ions in the intracellular and extracellular fluid of nerve cells, and by the selective permeability of the membrane to K^+ and Na^+ depending on the voltage and time. There is a much greater concentration of K^+ in the protoplasm of the nerve cell than in the extracellular fluid. But concentrations of Na^+ and Cl^- are less in the protoplasm than extracellular fluid. At rest the permeability of K^+ is much greater than Na^+. By their experiment, Hodgkin and Katz (1949) [25] suggested that during the action potential, the permeability of membrane to Na^+ increases transiently to become temporarily greater than the permeabilities to both K^+ and Cl^-. Further Hodgkin (1951) suggested that there is a subsequent increase in K^+ permeabilities.

This leads to a faster re-polarization of the membrane. This mechanism ultimately leads to the famous Hodgkin-Huxley Equations. During this time (increase in K^+ permeability and the suppression of Na^+ permeability during the final stage of the action potential), an additional action potential cannot be succeeded. This phenomenon is called *refractoriness* of the nerve cell. This period is called *refractory period* [3].

3. SPACE-CLAMPED HODGKIN-HUXLEY MODEL

Definition 3.1 (Space-clamped situation)**.** *Space-clamp technique was introduced by Marmont and Cole in 1949 to maintain a uniform voltage over a patch of nerve membrane. In space-clamped situation the voltage change of the action potential could occur simultaneously at every point along the squid axon as if it were in a patch instead of propagating in an axon. In other words,the space clamp situation eliminates voltage gradients along the axon. In this technique longitudinal voltage gradient is eliminated by threading the nerve patch with silver wires because silver has very low resistance. With the space clamp technique, Marmont was able to study the so called membrane action potentials. Mathematically, in the space-clamped situation, the model describing the voltage change becomes the ordinary differential equation instead of partial differential equations because now the voltage varies with respect to time only instead of both space and time.*

Definition 3.2 (Voltage-clamped situation)**.** *Voltage-clamped situation is to maintain membrane potential at any desired voltage level across a patch of membrane. Cole and colleagues developed a method for voltage-clamp which is electro-physiological technique to measure ion currents across the cell membrane. Under voltage clamp situation, voltage-gated ion channels open and close as normal, but the voltage clamp apparatus compensates for the changes in the ion current to maintain a constant membrane potential. This requires monitoring voltage changes, which was fed through an amplifier, to then run current into or out of the cell to maintain the voltage, while recording the current required to do so.*

Hodgkin, Huxley and Katz developed the voltage-clamped circuit to study the conductance properties of nerve axon of squid and found that the current through the membrane could be divided into the components of capacitative and ionic currents. For a small patch of membrane, the total current is

$$I_m = C_m \frac{dE}{dt} + I_i.$$

Here, E is the membrane potential, C_m is the capacitance of the membrane and I_i is the ionic current. Experiments showed that the ionic current was at first inward then followed by a persistent outward current. Hodgkin and Huxley used ionic substitution to separate the ionic current into its components; an inward current carried by Na^+ and outward current carried by K^+. The total ionic current can be expressed as

$$I_i = I_K + I_{Na} + I_L.$$

They considered the patch of the nerve axon, in space-clamped situation, as an electrical circuit in which the membrane capacitance C_m is parallel with the resistances corresponding to Na^+, K^+ and Cl^- which are the reciprocals of the respective conductances. As the

circuit is parallel, the total current can be expressed as

$$I = I_C + I_K + I_{Na} + I_L.$$

Here, I_C is capacitative current, I_K (Potassium current), I_{Na} (Sodium current) I_L (Leakage current carried by mainly chlorine ion) are ohmic currents (current through resistances). The driving potentials across these resistances are $E - E_K$, $E - E_{Na}$ and $E - E_L$, respectively, where E, E_K, E_{Na} and E_L are the membrane potential and equilibrium potentials of corresponding ions respectively. The total current is given by

$$I = C_m \frac{dE}{dt} + g_{Na}(E - E_{Na}) + g_K(E - E_K) + g_L(E - E_L).$$

Here $g_{Na},\ g_K,\ g_L$ are the conductances of the membrane for the respective ions. g_{Na}, g_K are assumed to be functions of voltage and time and g_L is constant. By using their voltage-clamp data, Hodgkin and Huxley fitted the Na^+ and K^+ conductances by

$$g_{Na} = g_{Na}^- m^3 h,\ g_K = g_K^- n^4,\ g_L = g_L^-$$

g_{Na}^-, g_K^- and g_L^- are constant conductances and $n,\ m,\ h$ are similar to the solution of

$$\frac{dy}{dt} = \alpha_y(1 - y) - \beta_y y.$$

Consider $V = E - E_r$, $V_{Na} = E_{Na} - E_r$, $V_K = E_K - E_r$ and $V_L = E_L - E_r$, where E_r is resting potential of membrane, then space-clamped Hodgkin-Huxley equations are

$$I_A(t) = C_m \frac{dV}{dt} + g_{Na}^- m^3 h(V - V_{Na}) + g_K^- n^4 (V - V_K) + g_L^-(V - V_L) \tag{3. 1}$$

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m \tag{3. 2}$$

$$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h \tag{3. 3}$$

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \tag{3. 4}$$

where I_A is applied current, V is the depolarization in the cell membrane, C_m is membrane capacitance, g_{Na}^-, g_K^- and g_L^- are constant conductances, V_K, V_{Na} and V_L are the equilibrium potentials, relative to the resting potential, of corresponding ions. In conformation with the existing literature [24, 36, 9], n denotes potassium activation, m, sodium activation, and h, sodium inactivation; moreover, these are dimensionless quantities taking values in [0,1] and at fixed V satisfy simple linear differential equations. $\alpha_m(V), \alpha_h(V), \alpha_n(V)$ and $\beta_m(V), \beta_h(V), \beta_n(V)$ are voltage-dependent constants. These constants were found

empirically and satisfactorily approximated by

$$\alpha_m(V) = \frac{25 - V}{10[e^{(25-V)/10} - 1]} \tag{3. 5}$$

$$\alpha_h(V) = \frac{7}{100} e^{-V/20} \tag{3. 6}$$

$$\alpha_n(V) = \frac{10 - V}{100[e^{(10-V)/10} - 1]} \tag{3. 7}$$

$$\beta_m(V) = 4e^{-V/18} \tag{3. 8}$$

$$\beta_h(V) = \frac{1}{e^{(30-V)/10} + 1} \tag{3. 9}$$

$$\beta_n(V) = \frac{1}{8e^{-V/80}}. \tag{3. 10}$$

Remark 3.3 (Sign convention for depolarization)**.** *In this paper, modern sign convention for membrane potential is used. As per modern convention, depolarization is positive as the membrane potential becomes more positive by depolarization. Tuckwell (1988)* [36]*, Christoph (2017)* [9] *and many other researchers used the modern convention in their work. But Hodgkin and Huxley* [24] *used the opposite sign convention and they consider depolarization negative. A detailed discussion about the convention is given in* [34].

4. Homotopy Perturbation Method

The Homotopy Perturbation Method merges two techniques i.e. the standard homotopy in topology and the perturbation techniques. We expect beginner level familiarity with the homotopy and perturbation technique, refer to [32, 8] for a standard introduction. To explain the HPM, consider a equation of the general type

$$A(u(x)) = 0,\ x \in D \tag{4. 11}$$

with its boundary conditions

$$B(u(x), \frac{\partial u}{\partial x}) = 0,\ x \in \omega \tag{4. 12}$$

where A is any differential or integral operator defined on domain D which is a finite subset of $\mathbb{R}^n$, x is an independent variable, B is boundary operator and ω is boundary of domain D. First, define a homotopy $H(u,p) : D \times [0,1] \longrightarrow \mathbb{R}$ by

$$H(u,p) = (1-p)[L(u) - L(u_0^-)] + pA(u) \tag{4. 13}$$

where $L(u)$ is a linear part of $A(u)$ and is easily invertible, u_0^- is an initial approximation of Equation 4. 11 which also satisfies the boundary condition given in Equation 4. 12 and $p \in [0,1]$. For $H(u,p) = 0$, it is obvious that

$$H(u,0) = L(u) - L(u_0^-) = 0,\ H(u,1) = A(u) = 0.$$

This shows that as the parameter p monotonically increases from 0 to 1, the linear problem $L(u) - L(u_0^-) = 0$ continuously deforms into the original problem $A(u) = 0$. Hence the initial approximation u_0^- continuously transform into the solution of the original problem.

Now, for applying the perturbation technique, consider the embedding parameter p as an expanding parameter. By expanding $u(x,p)$ in a series with respect to p, we have

$$u(x,p) = \sum_{i=0}^{\infty} p^i u_i = u_0 + pu_1 + p^2 u_2 + p^3 u_3 + \cdots \tag{4. 14}$$

If $p \to 1$, then $u(x,p)$ becomes the solution of Equation 4. 11 of the form

$$u(x) = \lim_{p\to 1} u(x,p) = \sum_{i=0}^{\infty} u_i = u_0 + u_1 + u_2 + \cdots \tag{4. 15}$$

By substituting Equation 4. 14 in $H(u,p) = 0$ and comparing the coefficients of equal powers of p, a set of simpler differential equations is obtained. By solving these equations recursively, we can find $u_0, u_1, u_2, \cdots$. Generally, series described in Equation 4. 15 is convergent and produces a closed form solution. The convergence of HPM is discussed in [2]. Approximate solutions of various orders can be obtained by truncating the series up to the required terms. In short, the mth order approximate solution of Equation 4. 11 can be written as

$$u(x) = \sum_{i=0}^{m} u_i = u_0 + u_1 + u_2 + \cdots + u_m.$$

5. Approximate Analytic Solution of Hodgkin-Huxley Model

5.1. **When a brief pulse of current is applied as a stimulus.** An impulse current as a stimulus is applied at $t = 0$ such that $I_A(t) = Q\delta(t)$ where Q is the charge delivered to the membrane and $\delta(t)$ is the delta function. So, $\frac{dV}{dt}$ is also a delta function. Hence, V has a jump at $t = 0$ to a value say V_0, also $\alpha's$ and $\beta's$ will also jump to their values at V_0. For this situation the space-clamped Hodgkin-Huxley model can be described as the following initial value problem.

$$C_m \frac{dV}{dt} + g_{\bar{N}a} m^3 h(V - V_{Na}) + g_{\bar{K}} n^4 (V - V_K) + g_{\bar{L}}(V - V_L) = 0, V(0) = V_0 \tag{5. 16}$$

$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n n, \qquad n(0) = n_0 \tag{5. 17}$$

$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m, \quad m(0) = m_0 \tag{5. 18}$$

$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h h, \qquad h(0) = h_0 \tag{5. 19}$$

Initial values of n,m and h are their resting steady-state values i.e. these are the asymptotic values of dimensionless variables n,m and h calculated at resting voltage level i.e. at $V = 0$. Asymptotic values of these variables can be calculated by $\frac{\alpha_n}{\alpha_n+\beta_n}$, $\frac{\alpha_m}{\alpha_m+\beta_m}$ and $\frac{\alpha_h}{\alpha_h+\beta_h}$ respectively. Hence, $n_0 = \frac{\alpha_n(0)}{\alpha_n(0)+\beta_n(0)} = 0.3$, $m_0 = \frac{\alpha_m(0)}{\alpha_m(0)+\beta_m(0)} = 0.05$ and $h_0 = \frac{\alpha_h(0)}{\alpha_h(0)+\beta_h(0)} = 0.6$.

Though Equations 5. 17 , 5. 18 and 5. 19 could be easily solved analytically but for the sake of completeness, we solved them here using Homotopy Perturbation Method.

For Equation 5. 19 we construct the homotopy equation by using the following homotopy. We take initial value of h as initial approximation solution of Equation 5. 19 i.e. $h_0^- = h_0$, hence $L(h_0^-) = 0$.

$$H(h,p) = (1-p)L(h) + pA(h).$$

Here

$$L(h) = \frac{dh}{dt},\ \&\ A(h) = \frac{dh}{dt} - \alpha_h(1-h) - \beta_h h.$$

$H(h,p) = 0$ gives $L(h) = p[L(h) - A(h)]$, which becomes

$$\frac{dh}{dt} = p[\alpha_h(1-h) - \beta_h h]$$

$$h - h_0 = p\int_0^t [\alpha_h(1-h) - \beta_h h]dt$$

By using perturbation technique, assume

$$h(t) = h_0(t) + ph_1(t) + p^2h_2(t) + \cdots$$

$$h_0(t) + ph_1(t) + p^2h_2(t) + \cdots = h_0 + p\int_0^t [\alpha_h - (\alpha_h + \beta_h)(h_0(t) + ph_1(t) + p^2h_2(t) + \cdots)]dt$$

On comparing same powers of p

$$\begin{aligned}
h_0(t) &= h_0\\
h_1(t) &= [\alpha_h - (\alpha_h + \beta_h)h_0]t\\
h_2(t) &= -(\alpha_h + \beta_h)[\alpha_h - (\alpha_h + \beta_h)h_0]t^2/2!\\
h_3(t) &= (\alpha_h + \beta_h)^2[\alpha_h - (\alpha_h + \beta_h)h_0]t^3/3!\\
h_4(t) &= -(\alpha_h + \beta_h)^3[\alpha_h - (\alpha_h + \beta_h)h_0]t^4/4!\\
&\vdots
\end{aligned}$$

As $p \to 1$,

$$\begin{aligned}
h(t) &= h_0(t) + h_1(t) + h_2(t) + \cdots\\
h(t) &= h_0 + [\alpha_h - (\alpha_h + \beta_h)h_0]t - (\alpha_h + \beta_h)[\alpha_h - (\alpha_h + \beta_h)h_0]t^2/2! +\\
&\quad (\alpha_h + \beta_h)^2[\alpha_h - (\alpha_h + \beta_h)h_0]t^3/3! - (\alpha_h + \beta_h)^3[\alpha_h - (\alpha_h + \beta_h)h_0]t^4/4! + \cdots\\
h(t) &= h_0 - \frac{[\alpha_h - (\alpha_h + \beta_h)h_0]}{(\alpha_h + \beta_h)}[e^{-(\alpha_h+\beta_h)t} - 1]\\
h(t) &= \frac{\alpha_h}{\alpha_h + \beta_h} + [h_0 - \frac{\alpha_h}{\alpha_h + \beta_h}]e^{-(\alpha_h+\beta_h)t}
\end{aligned}$$

The proof of uniform convergence of above series of functions is given in subsection 5.5.

Suppose,

$$\frac{\alpha_h}{\alpha_h+\beta_h}=h_\infty, \qquad \frac{1}{\alpha_h+\beta_h}=\tau_h \tag{5. 20}$$

Here, τ_h is time constant and h_∞ is asymptotic value of h. Then,

$$h(t)=h_\infty+(h_0-h_\infty)e^{\frac{-t}{\tau_h}}. \tag{5. 21}$$

Similarly,

$$m(t)=m_\infty+(m_0-m_\infty)e^{\frac{-t}{\tau_m}}. \tag{5. 22}$$

$$n(t)=n_\infty+(n_0-n_\infty)e^{\frac{-t}{\tau_n}}. \tag{5. 23}$$

Now consider Equation 5. 16 and construct the homotopy equation by using the following homotopy. We take initial value of V as initial approximation solution of Equation 5. 16 i.e. $V_0^-=V_0$, hence $L(V_0^-)=0$.

$$H(V,p)=(1-p)L(V)+pA(V).$$

Here

$$L(V)=C_m\frac{dV}{dt},\ \&$$
$$A(V)=C_m\frac{dV}{dt}+g_{Na}m^3h(V-V_{Na})+g_Kn^4(V-V_K)+g_L(V-V_L).$$

$H(V,p)=0$ implies

$$(1-p)L(V)+pA(V)=0$$
$$L(V)=p[L(V)-A(V)].$$

Which becomes

$$C_m\frac{dV}{dt}=p[C_m\frac{dV}{dt}-C_m\frac{dV}{dt}-g_{Na}m^3h(V-V_{Na})-g_Kn^4(V-V_K)-g_L(V-V_L)]$$
$$C_m\frac{dV}{dt}=p[-g_{Na}m^3h(V-V_{Na})-g_Kn^4(V-V_K)-g_L(V-V_L)].$$

It is clear that for $p=0$ above equation becomes the linear problem $\frac{dV}{dt}=0$ and for $p=1$, it becomes the equation we want to solve.
Integration both sides gives

$$C_mV-C_mV_0=-p\int_0^t[g_{Na}^-m^3h(V-V_{Na})+g_K^-n^4(V-V_K)+g_L^-(V-V_L)]dt.$$

By using perturbation technique, suppose,

$$V(t)=V_0(t)+pV_1(t)+p^2V_2(t)+\cdots$$

$$C_m(V_0(t)+pV_1(t)+p^2V_2(t)+p^3V_3(t)+\cdots)=C_mV_0+p\int_0^t[g_{Na}^-m^3h(V_{Na}-V_0(t)-pV_1(t)-p^2V_2(t)-\cdots)$$
$$g_K^-n^4(V_K-V_0(t)-pV_1(t)-p^2V_2(t)-\cdots)+g_L^-(V_L-V_0(t)-pV_1(t)-p^2V_2(t)-\cdots)]dt.$$

On comparing same powers of p,

$$V_0(t) = V_0$$

$$C_m V_1(t) = g_{Na}^- \int_0^t m^3 h(V_{Na} - V_0)dt + g_K^- \int_0^t n^4(V_K - V_0)dt + g_L^- \int_0^t (V_L - V_0)dt \tag{5. 24}$$

$$C_m V_1(t) = g_{Na}^-(V_{Na} - V_0) \int_0^t m^3 h dt + g_K^-(V_K - V_0) \int_0^t n^4 dt + g_L^-(V_L - V_0) \int_0^t dt \tag{5. 25}$$

$$C_m V_2(t) = -g_{Na}^- \int_0^t m^3 h V_1 dt - g_K^- \int_0^t n^4 V_1 dt - g_L^- \int_0^t V_1 dt \tag{5. 26}$$

$$C_m V_3(t) = -g_{Na}^- \int_0^t m^3 h V_2 dt - g_K^- \int_0^t n^4 V_2 dt - g_L^- \int_0^t V_2 dt \tag{5. 27}$$

$$C_m V_4(t) = -g_{Na}^- \int_0^t m^3 h V_3 dt - g_K^- \int_0^t n^4 V_3 dt - g_L^- \int_0^t V_3 dt \tag{5. 28}$$

$$\vdots$$

We can find V_1 from Equation 5. 25 by computing the integrals in it. Higher order solution can be found recursively. V_2 can be found by putting V_1 in Equation 5. 26 , and then perform integration, and recursively V_3 can be found by putting V_2 in equation 5. 27 and perform integration, and $V_4, V_5, \cdots$ etc can be computed similarly.
As $p \to 1$,

$$V(t) = V_0(t) + V_1(t) + V_2(t) + \cdots$$

Higher order solution involves lengthy cumbersome integration, hence this work is restricted to first order solution. For first order solution $V = V_0 + V_1$. Hence,

$$\begin{aligned} V(t) =& V_0 + \frac{1}{C_m}[g_K^-(V_K - V_0)n_\infty^4(t + \tau_n \sum_{k=1}^{4} \binom{4}{k} \frac{(\frac{n_0}{n_\infty} - 1)^k}{k}(1 - e^{\frac{-kt}{\tau_n}})) + \\ & g_{Na}^-(V_{Na} - V_0)hm_\infty^3(t - \tau_m \sum_{k=1}^{3} \binom{3}{k} \frac{(\frac{m_0}{m_\infty} - 1)^k}{k} e^{\frac{-kt}{\tau_m}}) + \\ & g_{Na}^-(V_{Na} - V_0)h_0 m_\infty^3 \tau_m \sum_{k=1}^{3} \binom{3}{k} \frac{(\frac{m_0}{m_\infty} - 1)^k}{k} + \\ & g_{Na}^-(V_{Na} - V_0)(h_0 - h_\infty)m_\infty^3 \tau_m \sum_{k=1}^{3} \binom{3}{k} \frac{(\frac{m_0}{m_\infty} - 1)^k}{k} \frac{\tau_m}{\tau_m + k\tau_h}(e^{-(\frac{1}{\tau_h} + \frac{k}{\tau_m})t} - 1) + \\ & g_{Na}^-(V_{Na} - V_0)(h_0 - h_\infty)m_\infty^3(-te^{\frac{-t}{\tau_h}} - \tau_h e^{\frac{-t}{\tau_h}} + \tau_h) + g_L^-(V_L - V_0)t]. \end{aligned} \tag{5. 29}$$

Values of parameters used are

$$C_m = 1\frac{\mu F}{cm^2},\ V_{Na} = 115mV,\ V_K = -12mV,\ V_L = 10.613mV$$
$$g_{Na}^- = 120\frac{m.mho}{cm^2},\ g_K^- = 36\frac{m.mho}{cm^2},\ g_L^- = 0.3\frac{m.mho}{cm^2}.$$

Initial values of n,m and h are their resting steady-state values i.e. $n_0 = 0.3,\ m_0 = 0.05,\ h_0 = 0.6$. These initial conditions are in the case when the impulsive current is applied to the nerve patch at rest. If initially, the nerve patch is voltage-clamped to some other value, then the initial conditions will be the asymptotic values of dimensionless variables calculated at that voltage level.

5.2. **When a constant sustained current is applied as a stimulus.** If a constant current density I_A is applied at $t = 0$ as a stimulus then the model will be as in Equations 3. 1 , 3. 2 , 3. 3 , 3. 4 . Initial conditions (if stimulus is applied when the membrane is at rest) corresponding to depolarization and activation variables would be their values at resting potential, i.e.$V_0 = 0$, $n_0 = 0.3$, $m_0 = 0.05$, $h_0 = 0.6$. Values of parameters are same as mentioned above. The approximate analytic solution of space-clamped Hodgkin-Huxley model for this situation is different only by a term from the solution of the model in a case where an impulsive current is applied as a stimulus. The solution for these equations with corresponding initial conditions is

$$\begin{aligned} V(t) =& V_0 + \frac{1}{C_m}[g_K^-(V_K - V_0)n_\infty^4(t + \tau_n \sum_{k=1}^{4}\binom{4}{k}\frac{(\frac{n_0}{n_\infty} - 1)^k}{k}(1 - e^{\frac{-kt}{\tau_n}})) + \\ & g_{Na}^-(V_{Na} - V_0)hm_\infty^3(t - \tau_m \sum_{k=1}^{3}\binom{3}{k}\frac{(\frac{m_0}{m_\infty} - 1)^k}{k}e^{\frac{-kt}{\tau_m}}) + \\ & g_{Na}^-(V_{Na} - V_0)h_0 m_\infty^3 \tau_m \sum_{k=1}^{3}\binom{3}{k}\frac{(\frac{m_0}{m_\infty} - 1)^k}{k} + \\ & g_{Na}^-(V_{Na} - V_0)(h_0 - h_\infty)m_\infty^3 \tau_m \sum_{k=1}^{3}\binom{3}{k}\frac{(\frac{m_0}{m_\infty} - 1)^k}{k}\frac{\tau_m}{\tau_m + k\tau_h}(e^{-(\frac{1}{\tau_h} + \frac{k}{\tau_m})t} - 1) + \\ & g_{Na}^-(V_{Na} - V_0)(h_0 - h_\infty)m_\infty^3(-te^{\frac{-t}{\tau_h}} - \tau_h e^{\frac{-t}{\tau_h}} + \tau_h) + (g_L^-(V_L - V_0) - I_A)t]. \end{aligned} \tag{5. 30}$$

It is worthy to note that the dimensionless variables, describing activation and inactivation of ionic conductances, were approximated empirically on the bases of voltage-clamp experiments, performed by Hodgkin and Huxley. Hence solution of the model inherits the effects of the voltage clamp situation even when the scenario is not voltage clamped. To offset or correct these effects approximate analytic solution is obtained in a piece-wise manner. To comply with this, the time domain is discretized in segments and the obtained approximate solutions are used to find the solution for each segment. The last value of voltage of a segment is used as the initial value of the voltage in the next segment. We apply the analytic technique on a temporal discretization using software (MATLAB). The procedure is given in the Algorithm 5.4.

5.3. **Algorithm for Approximate Analytic Solution of Hodgkin-Huxley Model.**

Algorithm 5.4. *This is the algorithm to calculate the approximate analytic solution of space-clamped Hodgkin-Huxley Equations for initial conditions* $V_0 = V(0),\ n_0 = n(0) = 0.3,\ m_0 = m(0) = 0.05,\ h_0 = h(0) = 0.6.$

j *is number of segments.*
$V_0(k)$ *is initial condition of* V *for* kth *segment.*
$m_0(k)$ *is initial condition of* m *for* kth *segment.*
$h_0(k)$ *is initial condition of* h *for* kth *segment.*
$n_0(k)$ *is initial condition of* n *for* kth *segment.*
for $k = 1$ *to* j ***do***
$V_0(k) \leftarrow V(k-1)$, $m_0(k) \leftarrow m(k-1)$, $h_0(k) \leftarrow h(k-1)$, $n_0(k) \leftarrow n(k-1)$
(1) Find values of αs *and* $\beta' s$ *corresponding to* $V_0(k)$ *by using Equations 3. 5 , 3. 6 , 3. 7 , 3. 8 , 3. 9 , and 3. 10 .*
(2) Find time constants τ_m, τ_h, τ_n *and asymptotic values* $m_\infty, h_\infty, n_\infty$ *of activation and non-activation variables corresponding to* $V_0(k)$ *by substituting the values of* $\alpha' s$ *and* $\beta' s$ *in Equations 5. 20 and similar dependency equations.*
(3) Find the value of activation and non-activation variables $m(k), h(k), n(k)$ *by substituting initial values (*$n_0(k), m_0(k), h_0(k)$*), time constants and asymptotic values of activation and non-activation variables corresponding to* $V_0(k)$ *in Equations 5. 21 , 5. 22 , and 5. 23 .*
(4) Obtain the value of first order analytic solution $V(k)$ *(depolarization) of this model by Equation 5. 29 (if stimulus is an impulse of current) or Equation 5. 30 (if stimulus is sustained constant current).*
end for

5.5. **Proof of Uniform Convergence of Series of Functions** $h_n(t)$**.** We use Abel's uniform convergence criterion for series of functions, Weierstrass M-test and Ratio test to prove the convergence of series of functions $h_n(t)$.

Theorem 5.6 (Abel's uniform convergence test)**.** *Let* g_n *be a uniformly bounded sequence of real-valued continuous functions on a set E such that* $g_{n+1}(x) \leq g_n(x)$ *for all* $x \in E$ *and positive integers* n*, and let* f_n *be a sequence of real-valued functions such that the series* $\sum_n f_n(x)$ *converges uniformly on* E*. Then* $\sum_n f_n(x)g_n(x)$ *converges uniformly on* E*.*

Theorem 5.7 (Weierstrass M-test)**.** *Let* f_n *be a sequence of functions* $f_n : E \to \mathbb{C}$ *and let* M_n *be a sequence of positive real numbers such that* $|f_n(x)| < M_n$ *for all* $x \in E$ *and* $n = 1, 2, 3, \ldots$*. If* $\sum_n M_n$ *converges, then* $\sum_n f_n$ *converges uniformly on* E*.*

Theorem 5.8 (Ratio Test)**.** *Suppose that* (a_n) *is a sequence of real numbers such that* a_n *is nonzero for all sufficiently large* $n \in N$ *and the limit* $r = \lim_{n\to\infty}(\frac{a_{n+1}}{a_n})$ *exists or diverges to infinity. Then the series* $\sum_{n=1}^{\infty} a_n$ *converges absolutely if* $0 \leq r < 1$ *and diverges if* $1 < r \leq \infty$*.*

To prove the convergence of $h(t) = h_0 + \sum_{n=1}^{\infty} h_n(t)$, we express the $h_n(t)$ in the form $f_n(t)g_n(t)$ i.e.

$$h_n(t) = [\alpha_h - (\alpha_h + \beta_h)h_0](-1)^{n-1}(\alpha_h + \beta_h)^{n-1}t^n/n!.$$

Here,

$$g_n(t) = [\alpha_h - (\alpha_h + \beta_h)h_0] \ \& \ f_n(t) = (-1)^{n-1}(\alpha_h + \beta_h)^{n-1}t^n/n!.$$

As, we applied HPM in a piece wise manner and due to voltage-clamped situation in each segment α_h and β_h are fixed quantities in the corresponding segment $[t_i, t_{i+1}]$. This implies that $g_n(t)$ is a constant sequence. Hence, $g_n(t)$ is uniformly bounded sequence of real valued continuous functions in the $[t_i, t_{i+1}]$ and also monotonic non-increasing (simultaneously non-decreasing) sequence. According to Abel's uniform convergence criterion we need to proof uniform convergence of $\sum_n f_n(t)$ in $[t_i, t_{i+1}]$.

To prove uniform convergence of $\sum_n f_n(t)$ in $[t_i, t_{i+1}]$, we use Weierstrass M-test. α_h and β_h are fixed quantities in the corresponding segment $[t_i, t_{i+1}]$ and $t < T$ where T is a fixed non- zero real number such that $T > t_{i+1}$ and if $M_n = (\alpha_h + \beta_h)^{n-1}T^n/n!$ then

$$|f_n(t)| < M_n \ \forall t \in [t_i, t_{i+1}] \ \& \ n = 1, 2, 3, \ldots.$$

For convergence of $\sum_n M_n$ we use Ratio Test.

$$r = \lim_{n\to\infty}(\frac{M_{n+1}}{M_n})$$

$$r = \lim_{n\to\infty}(\frac{(\alpha_h + \beta_h)^n T^{n+1}/(n+1)!}{(\alpha_h + \beta_h)^{n-1}T^n/n!})$$

$$r = \lim_{n\to\infty}(\frac{(\alpha_h + \beta_h)T}{(n+1)})$$

Hence, $r = 0$ implies the convergence of $\sum_n M_n$ and eventually the convergence of $h(t) = h_0 + \sum_{n=1}^{\infty} h_n(t)$.

6. Results & Discussion

In Figure 1, first order HPM solution of space-clamped Hodgkin-Huxley Equations for impulsive current as a stimulus, is plotted for $V_0 = 3$, $V_0 = 4$, $V_0 = 5$, $V_0 = 7$, $V_0 = 12$, $V_0 = 30$, $V_0 = 60$, $V_0 = 90$.In Figure 2 numerical solution obtained by second order midpoint method is shown. The first order approximate analytic solution that we compute through Algorithm 5.4 is consistent with the numerical solution obtained by second order midpoint method (MPM). The absolute difference between two methods for various initial values at $\Delta t = 0.005$ are presented in Table 1.

It is clear that for small initial depolarization (3mV or 4mV) the calculated membrane depolarization returns to zero and then a hyperpolarization follows. Curves corresponding to these initial depolarizations describe the sub-threshold response. For a slightly larger initial depolarization (5mV), depolarization increases and eventually attains a peak value of about 110mV and thereafter returns to zero and overshoot it to give after-hyperpolarization and then rises again to reach at resting state. Threshold value is somewhere between 4mV and 5mV. Curve corresponding to initial depolarizations of 5mV, 7mV, 12mV, 30mV, 60mV and 90mV respectively describe the action potential effect. Patterns of trajectories show that initially dV/dt is negative then for slightly larger initial depolarization an action potential develops. These results are significantly consistent with the existing results [24]. The plots of the solution for sustained currents $I_A = 10\mu A/cm^2$ and $I_A = 0.2\mu A/cm^2$ are given

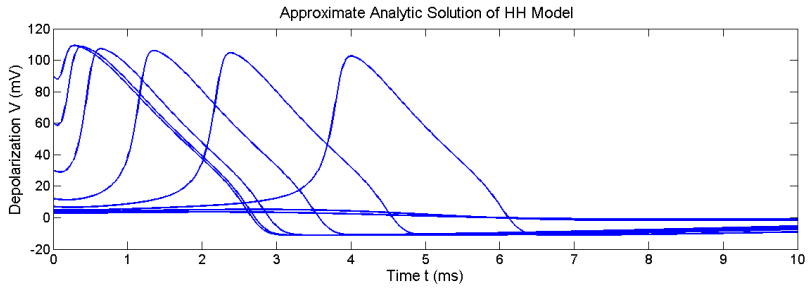

FIGURE 1. First order HPM solution of Hodgkin-Huxley model for various initial depolarizations.

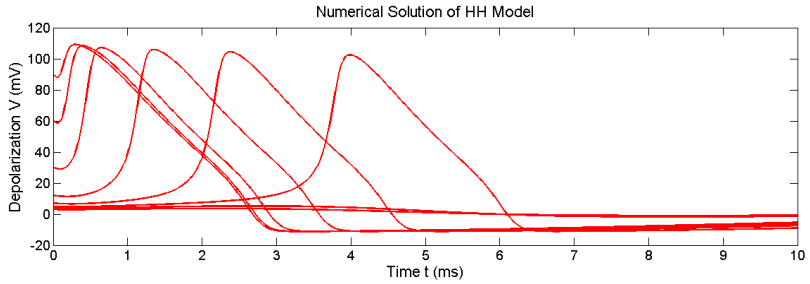

FIGURE 2. Second order numerical solution of Hodgkin-Huxley model by midpoint method for various initial depolarizations.

t	$\Delta(V_0 = 3)$	$\Delta(V_0 = 4)$	$\Delta(V_0 = 5)$	$\Delta(V_0 = 7)$	$\|\Delta(V_0 = 12)$	$\Delta(V_0 = 30)$
1	8.34E-5	2.0E-4	2.0E-4	2.0E-4	5.0E-4	7.3E-3
2	4.58E-5	1.0E-4	1.0E-4	5.0E-4	4.0E-4	5.61E-2
3	9.35E-5	1.0E-4	2.0E-4	0.0	3.59E-2	9.2E-3
4	4.82E-5	0.0	2.0E-4	3.1E-3	3.956E-1	3.12E-2
5	4.42E-5	3.0E-4	1.0E-3	1.16E-2	2.197E-1	4.16E-2
6	1.49e-4	6.0E-4	2.3E-3	3.66E-2	6.57E-2	4.54E-2
7	2.457e-4	1.0E-3	4.2E-3	1.323E-1	9.33E-2	4.52E-2
8	3.227e-4	1.4E-3	7.3E-3	7.142E-1	9.82E-2	4.36E-2
9	3.729e-4	1.9E-3	1.23E-2	1.0258	9.26E-2	4.21E-2
10	3.929e-4	2.4E-3	2.14E-2	1.511E-1	8.47E-2	4.21E-2

TABLE 1. Difference between analytic solutions by HPM and numerical solution by MPM on $\Delta t = 0.005$.

in Figure 3 and Figure 5 respectively. In Figure 4 and Figure 6, the numerical solutions by midpoint method of these situations are given. It can be observed easily that solutions by both methods match.

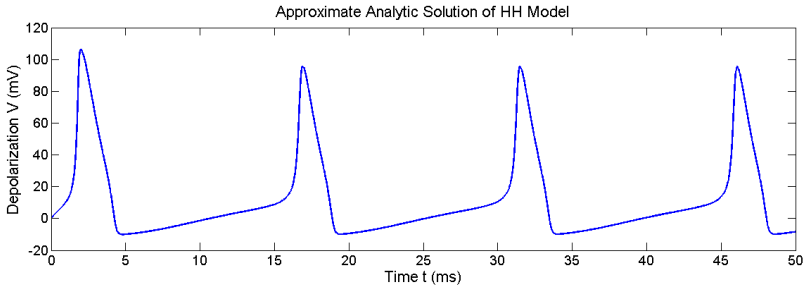

FIGURE 3. First order HPM solution of Hodgkin-Huxley model for a constant current $I_A = 10\mu A$ is applied as a stimulus.

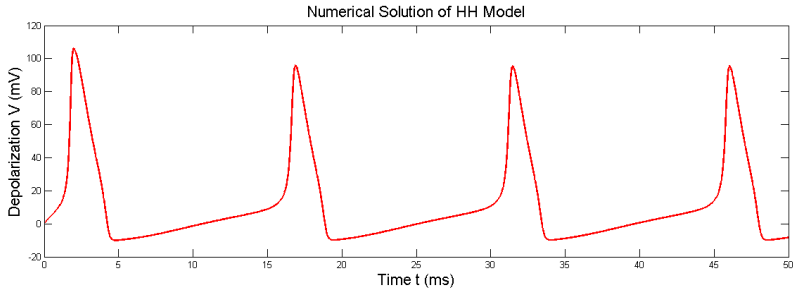

FIGURE 4. Second order numerical solution of Hodgkin-Huxley model for a constant current density $I_A = 10\mu A/cm^2$ is applied as a stimulus.

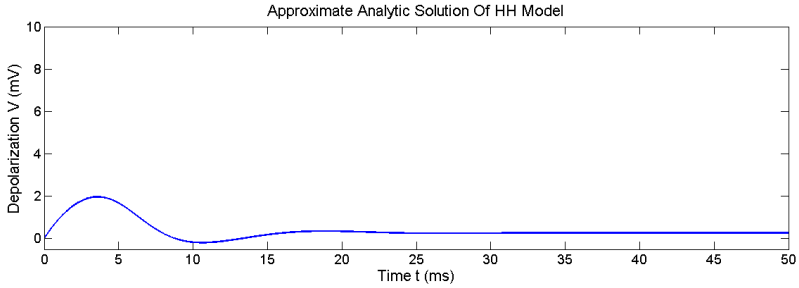

FIGURE 5. First order HPM solution of Hodgkin-Huxley model for a constant current density $I_A = 0.2\mu A/cm^2$ is applied as a stimulus.

It is observed that for sustained input current, these situations may arise, (1) train of several action potentials (Figure 3 & Figure 4) (some time only one action potential may occur) and (2) sub-threshold oscillations (Figure 5 & Figure 6). For sufficient constant applied current density (greater than or equal to threshold value), repetitive firing (spikes) is observed as shown in Figure 3 and Figure 4. Refractory period between two action potentials can be observed. It is observed that variation in the applied constant current affects the frequency

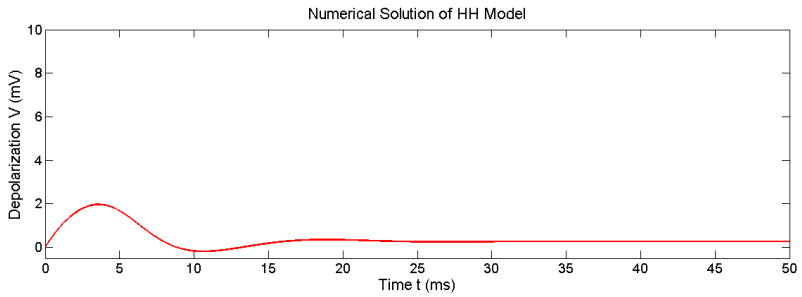

FIGURE 6. Second order numerical solution of Hodgkin-Huxley model for a constant current density $I_A = 0.2\mu A/cm^2$ is applied as a stimulus.

and amplitude of the oscillation. Insufficient constant applied current density produces few sub-threshold oscillations in the potential and then return to resting potential as shown in Figure 5 and Figure 6. These results are also consistent with the experimental and theoretical results.

7. CONCLUSION AND OUTLOOK

This work shows that Homotopy Perturbation Method is an easy and efficient method to find exact or approximate analytic solution of complex physical problems like Hodgkin-Huxley model. Even first order approximate solution has excellent agreement with the second order numerical solution found by midpoint method. Moreover, the approximate analytic solution recovers most of the key properties such as, the threshold potential, the action potential and the refractory period. We also solved this model by Adomian Decomposition Method and Variation Iteration Method, though that is not included in this paper. Analytic solution by these three methods are consistent but HPM is less cumbersome as compared to ADM and VIM, as in ADM we need to calculate Adomian Polynomials and in VIM we need to find Lagrange multiplier.

This work consists of approximate analytic solution of space-clamped Hodgkin-Huxley model which is a system of four nonlinear ordinary differential equations. Space-clamped model depicts only the partial picture of neuron's dynamical behavior as a result of an applied stimulus, as it describes the change in voltage only with respect to time. A more realistic understanding of nerve pulse propagation could be achieved by *full* or *complete* Hodgkin-Huxley model which is a system of four nonlinear partial differential equations. This model describes the change in voltage with respect to both time and space. An extension of this work to include the full set of Hodgkin-Huxley partial differential equations is underway.

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DECLARATIONS OF INTEREST

None.

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