Influence of Sodium Inward Current on Dynamical Behaviour of Modified Morris-Lecar Model

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Abstract This paper presents a modified Morris-Lecar model by incorporating the sodium inward current. The dynamical behaviour of the model in response to key parameters is investigated. The model exhibits various excitability properties as the values of parameters are varied. We have examined the effects of changes in maximum ion conductances and external current on the dynamics of the membrane potential. A detailed numerical bifurcation analysis is conducted. The bifurcation structures obtained in this study are not present in existing bifurcation studies of original Morris-Lecar model. The results in this study provides the interpretation of electrical activity in excitable cells and a platform for further study.

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1 Introduction

The variation in concentration of ions across the cell membrane results in fluxes of ions through the voltage-gated ion channels. This electrophysiological process in the cell membrane plays a fundamental role in understanding the electrical activities in excitable cells such as neurons (Mondal et al. 2019), muscle cells (Gonzalez-Fernandez and Ermentrout 1994) and hormones (Iremonger and Herbison 2020). The temporal variation of the cell membrane potential due to external stimulation is known as an action potential. Different ion channels play different roles in the generation of an action potential. Depending on the cell, the opening of Na\(^{+}\) (Ca\(^{2+}\)) channels causes influx of Na\(^{+}\) (Ca\(^{2+}\)) and the membrane potential becomes more positive, hence the membrane is depolarised. When the K\(^{+}\) channels are open, there is efflux of K\(^{+}\) which results in the repolarisation of the cell. Later, the membrane potential becomes more negative than the resting potential and the membrane is hyperpolarised. At this stage, the membrane will not respond to stimulus until it returns to the resting potential (Izhikevich 2007; Ermentrout and Terman 2008; Keener and Sneyd 2009; Fatoyinbo 2020).

From the viewpoint of mathematics, numerous mathematical models have been developed to study the nonlinear dynamics involved in the generation of an action potential in the cell membrane. They are often modelled by a nonlinear system of ordinary differential equations (ODEs). Among the famous works is the one by Hodgkin and Huxley (1952) on the conduction of electrical impulses along a squid giant axon. In their experiments, it was reported that action potentials depends on the influx of Na\(^{+}\). This work laid foundation for other electrophysiological models. Other well-known models are the FitzHugh-Nagumo model (1961; 1962), the Morris-Lecar
ML model describes the electrical activities of a giant barnacle muscle fibre membrane. Despite being a model for muscle cell, it has been widely used in modelling electrical activities in other excitable cells mostly in neurons (Azizi and Mugabi 2020; Jia 2018; Prescott et al. 2006; Zhao and Gu 2017). Based on experimental observations, ML model is formulated on the assumption that the electrical activities in barnacle muscle depend largely on fluxes of Ca\(^{2+}\) and K\(^{+}\) rather than Na\(^{+}\). On this basis, their model consists of three ODEs. It is observed that the Ca\(^{2+}\) current activates faster than the K\(^{+}\) current and the charging capacitor (Keynes et al 1973). Thus, the model is further reduced to two ODEs by setting the Ca\(^{2+}\) activation to quasi-steady state.

The two-dimensional ML model has been extensively used in many single-cell models (Wang et al. 2011; Lv et al. 2016; Upadhyay et al. 2017; Fatoyinbo et al. 2020) and network of cells (Fujii and Tsuda 2004; Lafranceschina and Wackerbauer 2014; Meier et al. 2015; Hartle and Wackerbauer 2017) studies despite it is an approximation of the three-dimensional ML model. In spite of little attention to the three-dimensional model, it has been used in modelling electrophysiological studies. For example, Gottschalk and Haney (2003) investigated how the activity of the ion channels are regulated by anaesthetics. The three-dimensional ML model was used by Marreiros et al. (2009) for modelling dynamics in neuronal populations using a statistical approach. Also, González-Miranda (2014) investigated pacemaker dynamics in ML model using the three-dimensional model. Gall and Zhou (1999) considered four-dimensional ML model by including the second inward Na\(^{+}\) current.

Many recent papers have studied modified ML model by adding relevant inward and outward ionic currents (Prescott et al. 2008; Duan et al. 2010; Meier et al. 2015; Bao et al. 2019; Azizi and Alali 2020). Zeldenrust et al. (2013) extended the ML model by including three additional ionic membrane currents: a T-type calcium current, a
cation selective h-current and a calcium dependent potassium current to investigate reliability of spikes in thalamocortical relay cells. Also, Azizi and Mugabi (2020) added calcium dependent potassium current to the ML model to study bursting properties in neurons. They showed that the model has complex dynamical behaviour including square-wave, elliptic, and parabolic busters depending on parameter combinations. Rajagopal et al (2021) modified the ML model by incorporating the influence of electric and magnetic field on dynamical behaviours of network of neurons. They found complex spatiotemporal dynamics including chaotic bursting and spiral waves.

The purpose of this paper is to investigate the influence of sodium inward currents on variation of membrane voltage of a single excitable cell. In recent years, experimental and computational analyses have suggested that sodium currents are relevant in the generation of action potential in some muscle cells (Jo et al 2004; Berra-Romani et al 2005; Ulyanova and Shirokov 2018). Bifurcation analysis is often used to investigate the mode of transition of electrical activities of excitable cells. It helps us to identify the key parameters that cause changes in the dynamical behaviour qualitatively (Kuznetsov Y. A. 1995; Keener and Sneyd 2009). A lot of studies on bifurcation analyses have been carried out on the two-dimensional (Govaerts and Sautois 2005; Tsumoto et al 2006; Prescott et al 2008; Fatoyinbo et al 2020) and three-dimensional (González-Miranda 2014) ML models, however, to our knowledge there appears no work in the literature that has extensively considered the bifurcation analysis of the four-dimensional ML model. In this present paper we focus on the maximum conductances of ion currents and external current as bifurcation parameters. As a consequence, we show some additional bifurcation that are not present in the existing results of ML model.

The paper is organised as follows. In Sect. 2, we present the model equations and the dynamics of the model upon variation of model parameters. A detailed bifurcation analyses are carried out in Sect. 3. Finally, the conclusion is presented in Sect. 4.
2 Model Equation

The classical Morris-Lecar (ML) model (1981) is a three-dimensional nonlinear system of ODEs, which is described as

\[
\frac{dV}{dt} = I_{\text{ext}} - I_L - I_{Ca} - I_K, \quad (1)
\]

\[
\frac{dm}{dt} = \lambda_m(V)(m_{\infty}(V) - m), \quad (2)
\]

\[
\frac{dn}{dt} = \lambda_n(V)(n_{\infty}(V) - n), \quad (3)
\]

where \( V \) is the membrane potential, \( I_{\text{ext}} \) is the external current, and \( C \) is the membrane capacitance. \( m \) and \( n \) are the fraction of open calcium and potassium channels, respectively. The ionic currents in (1) are defined as

\[
I_L = g_L(V - v_L), \quad I_{Ca} = g_{Ca}m(V - v_{Ca}), \quad I_K = g_{K}n(V - v_K), \quad (4)
\]

where \( g_L, g_{Ca}, \) and \( g_K \) are the maximum conductances of the leak, calcium, and potassium channels, respectively. Also \( v_L, v_{Ca}, \) and \( v_K \) are the Nerst reversal potentials of the leak, \( \text{Ca}^{2+}, \text{K}^{+} \), and \( \text{Na}^{+} \) channels, respectively.

Taking into account the contribution of \( \text{Na}^{+} \) on membrane depolarisation, we extend the ML model by adding \( \text{Na}^{+} \) current, \( I_{Na} = g_{Na}w(V - v_{Na}) \), in (1). With this current the ML model becomes a four-dimensional system of ODEs defined as

\[
\frac{dV}{dt} = I_{\text{ext}} - I_L - I_{Ca} - I_K - I_{Na}, \quad (5)
\]

\[
\frac{dm}{dt} = \lambda_m(V)(m_{\infty}(V) - m), \quad (6)
\]

\[
\frac{dn}{dt} = \lambda_n(V)(n_{\infty}(V) - n), \quad (7)
\]

\[
\frac{dw}{dt} = \lambda_w(V)(w_{\infty}(V) - w). \quad (8)
\]

The equivalent circuit representation of the cell membrane with four ionic channels, \( I_L, I_{Ca}, I_K, \) and \( I_{Na} \), is shown in Fig. 2.1. The fraction of open \( \text{Ca}^{2+}, \text{K}^{+} \) and \( \text{Na}^{+} \)
channels at steady state, denoted by $m_\infty$, $n_\infty$, and $w_\infty$, are defined as

$$m_\infty(V) = 0.5 \left( 1 + \tanh \left( \frac{V - \bar{v}_1}{\bar{v}_2} \right) \right),$$

$$n_\infty(V) = 0.5 \left( 1 + \tanh \left( \frac{V - \bar{v}_3}{\bar{v}_4} \right) \right),$$

$$w_\infty(V) = 0.5 \left( 1 + \tanh \left( \frac{V - \bar{v}_5}{\bar{v}_6} \right) \right).$$

The voltage-dependent rate constants associated with calcium, potassium and sodium channels are

$$\lambda_m(V) = \psi_m \cosh \left( \frac{V - \bar{v}_1}{2\bar{v}_2} \right),$$

$$\lambda_n(V) = \psi_n \cosh \left( \frac{V - \bar{v}_3}{2\bar{v}_4} \right),$$

$$\lambda_w(V) = \psi_w \cosh \left( \frac{V - \bar{v}_5}{2\bar{v}_6} \right).$$

Unless stated otherwise, parameter values are as listed in Gall and Zhou (1999): $C = 1$, $I_{\text{ext}} = 50, g_L = 2, v_L = -50, g_{\text{Ca}} = 4, v_{\text{Ca}} = 100, g_K = 8, v_K = -70, g_{\text{Na}} = 2, v_{\text{Na}} = 55, v_1 = -1, v_2 = 15, v_3 = 10, v_4 = 14.5, v_5 = 5, v_6 = 15, \psi_m = 1, \psi_n = 0.0667, \psi_w = 0.033.$
2.1 Changes to Excitable Dynamics as a Parameter is Varied

To analyse the model, we first assess the effects of Na\(^+\) current on electrical activity. To do this, we block the conductance \(g_{\text{Na}}\) for the Na\(^+\) current. The model is integrated numerically using the standard fourth-order Runge–Kutta method using a step size of 0.05 in the numerical software XPPAUT (Ermentrout 2002). Fig. 2.2a and 2.2b show the time series of the membrane potential \(V\) for model (5)–(8) when the Na\(^+\) conductance is blocked and unblocked, respectively. Over a range of parameters considered, we found that the addition of Na\(^+\) current causes the membrane potential to shift to more hyperpolarised values for hyperpolarised states, see Fig. 2.2b. This tells us that the effects of Na\(^+\) conductance is non-negligible.

![Fig. 2.2 Time series of the membrane potential \(V\) when the Na\(^+\) conductance \(g_{\text{Na}}\) is: (a) blocked \((g_{\text{Na}} = 0)\); (b) unblocked \((g_{\text{Na}} \neq 0)\) ](image-url)

As seen in previous studies (González-Miranda 2014; Fatoyinbo et al 2020), variation of parameters can result in changes to dynamical behaviour of the model, for example, transitions from rest state to periodic oscillations and vice versa. Here, we investigate the effects of maximum conductance on the dynamical behaviour of model (5)–(8). The dynamics of the membrane potential \(V\) upon varying Na\(^+\) current conductance \(g_{\text{Na}}\) is shown in Fig. 2.3. For the range of values of \(g_{\text{Na}}\) considered, the
system either converge to a rest state or oscillatory state. For extremely low values of $g_{Na}$, a single action potential is observed. In particular, the time evolution and its corresponding phase space for $g_{Na} = -20$ are shown in Figs. 2.3a and 2.3b, respectively. Upon increasing $g_{Na}$, periodic oscillations of action potentials are observed in the system, see Fig. 2.3c. The periodic oscillations correspond to a closed loop in the phase space, see Fig. 2.3d. The closed loop is also known as a limit cycle or periodic orbit. Further increasing $g_{Na}$, the system stabilises to a steady state, see Figs. 2.3e and 2.3f. Similar behaviours are observed when $g_K$ and $g_{Ca}$ are varied (results not shown). A detailed bifurcation analysis is given in Sec. 3 to further understand how the dynamical properties of model (5)–(8) change as parameter values is varied.

3 Numerical Bifurcation Analysis

With the aid of bifurcation analysis, we examine the dynamical behaviour of model (5)–(8) as different model parameters are varied in turn. The bifurcation diagrams are produced in XPPAUT and edited in MATLAB. The continuation parameters used in XPPAUT are $NTST=100$, $NMAX=2000$, $Method=stiff$, $EPSL=1e-7$, $EPSU=1e-7$, $EPSS=1e-7$, $ITMX=20$, $ITNW=20$, $DSMIN=1e-05$, $DSMAX=0.05$. The abbreviations and labels for the bifurcation points are given in Table 3.1.

Table 3.1 Abbreviations and notations of bifurcation points

| Bifurcation                  | Abbreviation |
|------------------------------|--------------|
| Hopf bifurcation             | HB           |
| Saddle-node bifurcation      | SN           |
| Saddle-node bifurcation of cycles | SNC       |
| Homoclinic bifurcation       | HC           |
| Period-doubling bifurcation  | PD           |
Fig. 2.3 Numerical simulations of the membrane potential $V$ for (a) $g_{Na} = -20$; (c) $g_{Na} = -10$; (e) $g_{Na} = 1.8$. Their corresponding phase space are (b), (d) and (f), respectively.

3.1 Influence of $g_{Na}$

Here, we vary $g_{Na}$ to explore the effects of Na$^+$ current on the dynamical behaviour of model (5)–(8). Fig. 3.1 is a bifurcation diagram of the membrane potential $V$ upon varying $g_{Na}$ with other parameters fixed. For the range of values of $g_{Na}$ considered,
there exists a unique equilibrium. The system has a stable equilibrium except between two Hopf bifurcations where the equilibrium is unstable. As seen in Fig. 3.1a, the system loses stability through a subcritical Hopf bifurcation HB\(_1\) at \(g_{Na} \approx -13.305\) and regains stability at another subcritical Hopf bifurcation HB\(_2\) at \(g_{Na} \approx 0.69436\). The unstable limit cycle generated at HB\(_1\) gain stability through a saddle-node bifurcation of cycle SNC\(_1\) at \(g_{Na} \approx -13.4394\), and loses stability at a period-doubling bifurcation PD\(_1\). The unstable limit cycle branch regains stability through another SNC\(_3\) at \(g_{Na} \approx -13.1223\). The stable double-period limit cycle branch emanated from the PD\(_1\) loses stability at another period doubling bifurcation PD\(_2\) at \(g_{Na} \approx -13.4323\), and it regains stability through a SNC\(_2\) at \(g_{Na} \approx -13.2516\) before converging to the first unstable limit cycle branch at \(g_{Na} \approx -13.1223\), see Fig. 3.1b. Upon further increasing the value of \(g_{Na}\), the limit cycle loses stability in a SNC\(_4\) at \(g_{Na} \approx 1.10527\) before it ends in a HB point at \(g_{Na} \approx 0.69436\).

Continuation of PD\(_2\) bifurcation results in another stable limit cycle that loses stability at a period doubling bifurcation PD\(_4\), the period of this limit cycle is double the period of the limit cycle of PD\(_2\). Continuing this process results in a cascade of PD bifurcations of limit cycles, and this may lead to chaotic dynamics in the system (Seydel 2010; Kügler et al 2017). Table 3.2 shows the values and period of the period doubling bifurcations that arise as \(g_{Na}\) is varied. The projection of the periodic trajectories for Period-1, 2, 4, 8, 16 and 32 onto \((V, n, m)\) phase space is illustrated in Fig. 3.2. All the double-period unstable limit cycles generated at each PD points undergo SNC bifurcations before they converge to the limit cycle emanated from the first HB bifurcation.

### 3.2 Influence of \(g_K\) and \(g_{Ca}\)

Fig. 3.3a shows the bifurcation diagram of the membrane potential \(V\) as \(g_K\) is varied. For the values of \(g_K\) considered, there exists a unique equilibrium. For extremely low
Fig. 3.1 (a) Bifurcation diagram of the membrane potential $V$ with $g_{Na}$ as bifurcation parameter. The remaining parameter values are fixed as in Sec. 2. (b)-(c) are enlargements of (a). Continuous [dashed] curves correspond to stable [unstable] solutions. Black [magenta] curves correspond to equilibria [periodic oscillations]. HB: Hopf bifurcation; SN: saddle-node bifurcation (of an equilibrium); SNC: saddle-node bifurcation of a periodic orbit; PD: period-doubling bifurcation.

Table 3.2 Summary of the parameter values and period of period-doubling bifurcations that arise as $g_{Na}$ is varied

| Bifurcation | $g_{Na}$  | Period  |
|-------------|-----------|---------|
| PD$_1$      | -13.4334  | 36.0272 |
| PD$_2$      | -13.4323  | 72.1846 |
| PD$_4$      | -13.4321  | 144.489 |
| PD$_8$      | -13.4320  | 289.001 |
| PD$_{16}$   | -13.4320  | 578.025 |
| PD$_{32}$   | -13.4320  | 1156.05 |
Fig. 3.2 Phase-space of (5)–(8) showing the cascade of period-doubling bifurcations. (a) Period-1 (b) Period-2 (c) Period-4 (d) Period-8 (e) Period-16 (f) Period-32, respectively.

values and high values of $g_K$, the equilibrium is stable. Increasing $g_K$, the system loses stability through a subcritical Hopf bifurcation $HB_1$ at $g_K \approx 10.029$ and this leads to emergence of an unstable limit cycle which becomes stable through a saddle node bifurcation of cycles $SNC_1$ at $g_K \approx 9.345$. As $g_K$ increases further, the stable limit cycle changes stability in another saddle node bifurcation of cycles $SNC_2$ at
$g_K \approx 46.598$. The unstable limit cycle ends in another subcritical Hopf bifurcation HB$_2$ at $g_K \approx 42.583$. Bistability is observed, that is, a stable limit cycle coexists with a stable equilibrium when $9.345 \leq g_K \leq 10.029$ and $42.583 \leq g_K \leq 46.598$.

![Bifurcation diagrams](image)

**Fig. 3.3 Bifurcation diagrams of the membrane potential $V$ with (a) $g_K$ (b) $g_{Ca}$ as the bifurcation parameters and other parameters are fixed as in Sec. 2. The labels and other conventions are as in Fig. 3.1**

Next, we vary the value of the parameter $g_{Ca}$. Fig. 3.3b shows the bifurcation diagram of the membrane potential $V$ as $g_{Ca}$ is varied. As $g_{Ca}$ is varied, the system loses stability through a subcritical Hopf bifurcation HB$_1$ at $g_{Ca} \approx 1.6191$ and this results in emergence of unstable limit cycle which becomes stable through a saddle node bifurcation of cycles SNC$_1$ at $g_{Ca} \approx 1.5974$. As $g_{Ca}$ increases further, the stable limit cycle loses stability in another saddle-node bifurcation SNC$_2$ at $g_{Ca} \approx 3.2579$ and the unstable limit cycle ends in a subcritical Hopf bifurcation HB$_2$ at $g_{Ca} \approx 2.8938$. Between the two subcritical Hopf bifurcations, there exists a unique unstable equilibrium point. For $1.5974 \leq g_{Ca} \leq 1.6191$ and $2.8938 \leq g_{Ca} \leq 3.2579$, a stable limit cycle coexists with a stable equilibrium and the system is bistable. For these values of $g_{Ca}$, a stable limit cycle coexists with a stable equilibrium.
3.3 Influence of $I_{\text{ext}}$

Apart from maximum conductance of ionic channels, the influence of external current is highly important while investigating the dynamics of action potentials in electrophysiological studies. Here, we consider the effects of $I_{\text{ext}}$ using two parameter sets. For set I, the parameter values are as listed in Sect. 2. Fig. 3.4a is a bifurcation diagram of the membrane potential $V$ with the applied current $I_{\text{ext}}$ as a bifurcation parameter, other parameters fixed. For very low value of $I_{\text{ext}}$, a unique stable equilibrium point exists. Upon increasing $I_{\text{ext}}$, the system changes stability through a saddle node bifurcation $\text{SN}_1$ at $I_{\text{ext}} \approx 30.52$ and the unstable branch fold back via another saddle node bifurcation $\text{SN}_2$ at $I_{\text{ext}} \approx -39.57$. Between the two SN bifurcations, the system has three equilibria: one stable (lower branch) and two unstable (upper and middle branch), see Fig. 3.4a. The upper unstable branch changes stability at a subcritical Hopf bifurcation $\text{HB}$ at $I_{\text{ext}} \approx 6.656$ before the system returns to a rest state as $I_{\text{ext}}$ increases. The unstable limit cycle emanated from $\text{HB}$ fold back and changes to a stable limit cycle through a saddle node bifurcation of cycles $\text{SNC}_1$ at $I_{\text{ext}} \approx 26.84$. The limit cycle loses stability at another $\text{SNC}_2$ at $I_{\text{ext}} \approx 22.99$ before it terminates at $I_{\text{ext}} \approx 23.79$.

For set II, $v_6 = 3$ while other parameters are fixed as in Sec. 2. A bifurcation diagram of the membrane potential $V$ with $I_{\text{ext}}$ as bifurcation parameter is shown in Fig. 3.5a. For $I_{\text{ext}} < -8.7715$, there exists a unique stable equilibrium point. Upon increasing $I_{\text{ext}}$, the system loses stability through a subcritical Hopf bifurcation $\text{HB}_1$ at $I_{\text{ext}} \approx 33.29650$. The unstable limit cycle emanated from $\text{HB}_1$ ends in an homoclinic bifurcation $\text{HC}_1$ at $I_{\text{ext}} \approx 33.2911$, see Fig. 3.5b. The curve of the homoclinic orbit is shown in Fig. 3.6a. Increasing $I_{\text{ext}}$ slightly there appears a saddle-node bifurcation $\text{SN}_1$ at $I_{\text{ext}} \approx 33.2026$, the unstable branch fold back at another saddle-node bifurcation $\text{SN}_2$ at $I_{\text{ext}} \approx -8.7715$. 
Fig. 3.4 (a) Bifurcation diagram of the membrane potential $V$ with $I_{\text{ext}}$ as the bifurcation parameter. and other parameters are fixed as in Sec. 2. The labels and other conventions are as in Fig. 3.1

As $I_{\text{ext}}$ increases further, the system passes through another saddle node bifurcation $\text{SN}_3$ at $I_{\text{ext}} \approx 0.8353$. For $I_{\text{ext}} \in [\text{SN}_2, \text{SN}_3]$, there exist three equilibria; one stable and two unstable. The branch of $\text{SN}_3$ bifurcation folds at another saddle-node bifurcation $\text{SN}_4$ at $I_{\text{ext}} \approx -1.7961$, and the unstable upper branch becomes stable in another subcritical Hopf bifurcation $\text{HB}_2$. For $I_{\text{ext}} \in [\text{SN}_4, \text{HB}_2]$, there exist five equilibria; one stable and four unstable equilibria. Also, for $I_{\text{ext}} \in [\text{HB}_2, \text{SN}_3]$, there exist five equilibria; two stable and three unstable. For this parameter values, the system is bistable, that is, coexistence of two stable equilibria. To the right of $\text{SN}_1$, the system has a unique stable equilibrium.

The unstable limit cycle generated at the Hopf bifurcation $\text{HB}_2$ fold back at $I_{\text{ext}} \approx 10.80$ and slightly after the fold point appears a period-doubling bifurcation $\text{PD}_1$ at $I_{\text{ext}} \approx 10.77$. At $\text{PD}_1$, the limit cycle bifurcates into unstable double-period and unstable limit cycles, and they both end in an homoclinic bifurcation, see Fig. 3.5c. The curve of the homoclinic orbit is shown in Fig. 3.6b. Continuation from the period-doubling $\text{PD}_1$ results in period-doubling bifurcation $\text{PD}_2$, subsequently, the $\text{PD}_2$ results in period-doubling bifurcation $\text{PD}_4$. Table 3.3 shows the parameter values for the period-doubling and homoclinic bifurcations and their corresponding periods as
Fig. 3.5 (a) Bifurcation diagram of membrane potential $V$ with $I_{\text{ext}}$ as a bifurcation parameter. (b)–(c) are enlargements of (a) and other parameters are fixed as in Sec. 2. The labels and other conventions are as in Fig. 3.1.

Fig. 3.6 The curves of homoclinic orbits of the periodic oscillation emanated at (a) $HB_1$; (b) $HB_2$. 

(a)

(b)

(c)
$I_{\text{ext}}$ is varied. The projections of periodic trajectories for period-1, 2, 4 onto $(V, n, m)$ phase space are shown in Fig. 3.7.

Table 3.3 Summary of the parameter values and period of period doubling and homoclinic bifurcations that arise as $I_{\text{ext}}$ is varied

| Bifurcation point | $I_{\text{ext}}$ | Period       |
|-------------------|------------------|--------------|
| PD₁               | 10.7705          | 33.5585      |
| PD₂               | 10.7584          | 67.1396      |
| PD₄               | 10.7555          | 134.353      |
| HC₁               | 33.2911          | 2.61499E+08  |
| HC₂               | -4.05553         | 3.95045E+09  |

3.4 Two Parameter Bifurcation Analysis

In this section we perform two parameter bifurcation analysis of (5)–(8) in $(I_{\text{ext}}, gK)$ plane. The bifurcation diagram shown in Fig. 3.10 is produced via numerical continuation software MATCONT (Dhooge et al 2003). The software implements Moore-Penrose continuation method to compute family and path of existing solution curves as parameters are varied. It is able to detect various kinds of bifurcations, switch to and compute the bifurcated branches, and allows us to follow the loci of the bifurcations in two parameters to detect codimension-2 bifurcation points. The step-by-step procedures for generating the codimension-2 bifurcation diagram Fig 3.10 in the GUI of MATCONT are given below:

i. First we integrate (5)–(8) from initial state variable values $(V, m, n, w) = (-20, 0, 0, 0)$ until the solution converges to an equilibrium point.

ii. Then we compute the equilibrium curve with $I_{\text{ext}}$ as continuation parameter. To initialise the equilibrium continuation from the last point in (i), we set $I_{\text{ext}} = 50$, ntst = 40, and ncol = 4 in the Starter window and then compute Forward and
Fig. 3.7 Phase-space of (5)–(8) showing the period-doubling bifurcations in response to variation of $I_{\text{ext}}$. (a) Period-1 (b) Period-2 (c) Period-4, respectively

**Backward.** Two Hopf bifurcations and four saddle-node bifurcations of equilibria are detected along the curve. The MATCONT window during the computation of the equilibrium curve is shown in Fig. 3.8.

iii. Next we compute the limit cycles from the Hopf bifurcations. In the Starter window we set $I_{\text{ext}}$ as bifurcation parameter and activate period to follow the period of oscillation along the continuation. We compute Forward to start the continuation from the Hopf bifurcation in the lower branch. MATCONT detects no special point except that the unstable limit cycle that emanates from the Hopf
bifurcation terminates at an homoclinic bifurcation, see Fig. 3.9a. Similarly, we compute **Forward** to start continuation from the Hopf bifurcation in the upper branch, an unstable limit cycle emanated from the Hopf bifurcation also terminated an homoclinic bifurcation and along the computation three period-doubling bifurcations are detected, see Fig. 3.9b.

Fig. 3.8 MATCONT window during the computation of the equilibrium curve

Fig. 3.9 A plot of the limit cycle that emanates from (a) the Hopf bifurcation in the lower branch; (b) the Hopf bifurcation in the upper branch of the equilibrium curve shown in Fig. 3.8
iv. Finally, in the Continuer window we set MaxStepSize = 1 and select \( I_{\text{ext}} \) and \( g_K \) as bifurcation parameters in the Starter window. We then compute Forward and Backward at the Hopf bifurcation to produce the Hopf locus. Similarly, the loci of the saddle-node bifurcation and period-doubling bifurcation are initialised from each bifurcation points, respectively. Several codimension-2 bifurcations are detected and their descriptions are explained in Table 3.4.

| Bifurcation                | Abbreviation |
|----------------------------|--------------|
| Cusp bifurcation           | CP \( i = 1,2,3 \) |
| Bogdanov-Takens bifurcation| BT \( i = 1, 2 \) |
| Generalized Hopf bifurcation| GH \( i = 1,2,3 \) |
| Zero-Hopf bifurcation      | ZH           |
| Generalised Period Doubling bifurcation | GPD \( i = 1,2 \) |
| 1:2 Resonance              | R2           |
| Flip-flop bifurcation      | LPPD         |

Table 3.4 Abbreviations of codimension-two bifurcations

Fig. 3.10 is divided into regions with respect to different types of dynamical behaviour and we have assigned each region a number, see Table 3.5. In the remainder of this section we describe the dynamics of model (5)–(8) as \( I_{\text{ext}} \) and \( g_K \) are varied.

For sufficiently large values of \( g_K \), there are two supercritical Hopf bifurcations \( HB_1 \) and \( HB_2 \). Thus for slice \( l_1 \) in Fig. 3.10 there are period solutions in region II. A codimension-1 bifurcation diagram along slice \( l_1 \) for which \( g_K = 60 \) is shown in Fig. 3.11a. The stable equilibrium solution loses stability through a Hopf bifurcation \( HB_2 \) as \( I_{\text{ext}} \) is varied. A stable limit cycle emanated from \( HB_2 \) ends in another Hopf bifurcation \( HB_1 \) before the equilibrium regains stability via \( HB_1 \). Here the system passes through regions I \( \rightarrow \) II \( \rightarrow \) I. As the value of \( g_K \) decreases, there appears a generalised Hopf bifurcation, denoted \( GH_1 \), on the Hopf bifurcation locus at \( g_K \approx 43.9007 \). This is a codimension-2 point where the HB locus changes from supercritical SupHB.
Fig. 3.10 Two parameter bifurcation diagram of (5)–(8) in the \((I_{\text{ext}}, g_K)\)-plane for parameter set II in Sect. 3.3 and other parameter values as in Sect. 2. The values of \(g_K\) in \(I_1, I_2, I_3, I_4\) are 60, 26, 8 and 3.5, respectively. The blue, red and magenta curves are the loci of Hopf bifurcation, saddle-node bifurcation, and period doubling bifurcation. The labels for the codimension-2 bifurcations are explained in Table 3.4. The invariant sets that exist in each region are listed in Table 3.5.

Table 3.5 Summary of the six different combinations of equilibria and limit cycles that arise in Fig. 3.10 and its magnifications, Figs. 3.12a, 3.12b, and 3.13a

| Region | Existence of equilibria and limit cycles |
|--------|----------------------------------------|
| I      | One stable equilibrium, no limit cycles (rest state). |
| II     | One unstable equilibrium, one stable limit cycle. |
| III    | One stable equilibrium, two unstable equilibria, no limit cycles. |
| IV     | Two stable equilibria, one unstable equilibrium, no limit cycles. |
| V      | One stable equilibrium, four unstable equilibria, one unstable limit cycle. |
| VI     | Two stable equilibria, three unstable equilibria, one unstable limit cycle. |
to subcritical SubHB (Kuznetsov Y. A. 1995). Below the GH₁, there are two Hopf bifurcations, a subcritical and a supercritical. Fig. 3.11b is a bifurcation diagram along slice l₂ in Fig. 3.10 for which \( g_K = 26 \). The system passes through regions I→II→I as in the previous case (slice l₁) except that the stable equilibrium solution in region I loses stability through a subcritical Hopf bifurcation HB₂. An unstable limit cycle emanated from HB₂ changes stability via a saddle-node bifurcation of limit cycles (SNC), the stable limit cycle ends in a supercritical Hopf bifurcation HB₁ then to the left of HB₁ the equilibrium solution regains stability.

![Fig. 3.11](image-url)

Fig. 3.11 (a) A codimension-1 bifurcation diagram along line l₁ with \( g_K = 60 \). (b) A codimension-1 bifurcation diagram along line l₂ with \( g_K = 26 \). The labels and other conventions are as in Fig. 3.1

Upon further decrease in the value of \( g_K \), the loci of saddle-node bifurcations SN₁ and SN₂ collide and annihilate in a cusp bifurcation CP₁ at \( g_K \approx 18.1715 \). As \( g_K \) decreases, a 1:2 resonance bifurcation R₂ and two generalised period-doubling bifurcations GPD₁ and GPD₂ appear on the locus of period doubling bifurcation at \( g_K \approx 12.624, 15.982, \) and 13.535, respectively. Also, the loci of saddle-node bifurcations SN₃ and SN₄ collide and annihilate in a cusp bifurcation CP₃ at \( g_K \approx 8.6962 \) and the supercritical Hopf bifurcation SupHB changes to subcritical Hopf bifurcation in another generalised Hopf bifurcation GH₂ at \( g_K \approx 11.3037 \), see Fig. 3.12a.
As the value of $g_K$ is decreased below CP$_3$, there exist four saddle-node bifurcations SN$_1$, SN$_2$, SN$_3$ and SN$_4$, an example is shown in Fig. 3.12b along slice $l_3$. The corresponding codimension-1 bifurcation diagram for which $g_K = 8$ is shown in Fig. 3.5a and described in Sec. 3.3. The system passes through regions I $\rightarrow$ III $\rightarrow$ V $\rightarrow$ VI $\rightarrow$ IV $\rightarrow$ I in Fig. 3.10. The loci of saddle-node bifurcations SN$_2$ and SN$_3$ collide and annihilate in a cusp bifurcation CP$_2$ at $g_K \approx 18.1715$. As we decrease the value of $g_K$ further, Bogdanov-Takens BT$_1$ and BT$_2$ occur on the loci of saddle-nodes SN$_2$ and SN$_1$ at $g_K \approx 7.1062$ and $g_K \approx 6.9935$, respectively. The loci of subcritical Hopf bifurcations emanate from these codimension-2 points. These loci are tangential to SN$_2$ and SN$_1$ at these codimension-2 points. Observe also are zero-Hopf bifurcation ZH at $g_K \approx 6.4099$, a codimension-2 where the locus of HB$_2$ intersect the locus of SN$_4$, and flip-flop bifurcation at $g_K \approx 6.8379$ on the locus of period doubling bifurcation as $g_K$ decreases.

Finally, as $g_K$ is decreased further a generalised Hopf bifurcation, denoted GH$_3$, occurs on the Hopf bifurcation locus HB$_2$ at $g_K \approx 4.1025$. Below this codimension-2 point, the only bifurcations that remain are the two saddle-node bifurcations SN$_1$ and SN$_2$. An example is shown Fig. 3.13a which is an enlargement of Fig. 3.10. A
bifurcation diagram along slice $l_4$ for which $g_K = 3.5$ is shown in Fig. 3.13b. Here the system passes through regions $I \rightarrow IV \rightarrow I$.

Fig. 3.13 (a) An enlargement of Fig. 3.10 showing lines $l_4$. (b) A codimension-1 bifurcation diagram along line with $g_K = 3.5$. The labels and other conventions are as in Fig. 3.10 and Table 3.4

4 Conclusion

In this present paper, we have studied a 4D-ML model to explore the influence of second inward Na$^+$ currents on electrical activities of excitable tissues. This work is motivated by the results in (Ulyanova and Shirokov 2018), where it is reported that voltage-gated Na$^+$ currents appear to contribute to the depolarising stage of action potentials in some excitable cells. We focused on addressing the influence of maximum conductances of ion channels on the dynamics of the membrane potential. Upon varying the conductance associated with the Na$^+$ currents, $g_{Na}$, the model exhibits different electrical activities.

With the aid of numerical bifurcation analysis, we examined the effects of parameters on the dynamical behaviour of the model. Our results showed that increasing the maximum conductance of sodium current $g_{Na}$, the model transitions from rest state
to periodic oscillations. For some values of $g_{Na}$, the model shows complex behaviour, specifically, it undergoes cascades of period-doubling bifurcations. It was found that the bifurcation structure of varying the maximum conductance of potassium current $g_K$ is qualitatively similar to that of varying the maximum conductance of calcium current $g_{Ca}$ except in reverse. That is, increasing the value of $g_K$ results in the same qualitative changes to the dynamics of the model as decreasing the value of $g_{Ca}$.

We also showed qualitatively the effect of varying the external current $I_{ext}$ on the dynamical behaviour of the model. Similar bifurcation diagram has been observed by Gall and Zhou (1999), they discussed the bifurcation diagram in some detail, although without an explicit determination of the period oscillations thus their bifurcation diagram seems incomplete. However, in this work, we give a detailed bifurcation structure. We showed that the unstable periodic oscillations emanated from the two Hopf bifurcations terminate in homoclinic bifurcations. We also observed cascades of period-doubling PD bifurcations for some values of $I_{ext}$. The existence of PD bifurcations is an indicator that the model can exhibit chaotic behaviour in some parameter regime.

The codimension-2 bifurcation analysis in $(I_{ext}, g_K)$-plane gives further details on transitions between different electrical activities in the model. The electrical activities in the original ML model can be of Type I or II excitability depending on how the cell transitions from rest state to periodic oscillations is through a Hopf bifurcation. (Fatoyinbo et al 2020; Tsumoto et al 2006). In Type I excitability, the cell transitions from rest to an oscillatory state via a saddle-node on an invariant circle bifurcation and in Type II excitability the transition is via a Hopf bifurcation. In this work, the model exhibits only Type II excitability.

The results in this paper showed that the Na$^+$ channels may influence the depolarisation stage of an action potential. It is hope that this model provides a framework that can aid in the understanding of various electrical activities in excitable cells. Based on the results of the present paper more complex behaviour is expected when
two or more cells are coupled together, thus the dynamics of a network of cells would be addressed in future. The individual systems can be interconnected via ring-star network (Muni and Provata 2020), two-dimensional lattice (Shepelev et al 2020), multilayer network (Shepelev et al 2021) to account for various other spatio temporal patterns, chimera states.

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Contributions

The presented idea was conceived by HOF. He wrote the MATCONT and XPPAUT codes. HOF and SSM carried out the numerical simulations and generated the figures. AA aided in the interpretation of the results. All authors jointly prepared the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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