

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.

Keywords: Excitable cells, Ion conductance, Morris-Lecar model, Period-doubling bifurcation

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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 [1], muscle cells [2] and hormones [3]. 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+}) ion 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 [4, 5, 6]. From the viewpoint of mathematics, numerous mathematical models have been developed to study the nonlinear

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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 [7] 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^+ and Ca^{2+} . This work laid foundation for other electrophysiological models. Other well-known models are the FitzHugh-Nagumo model [8, 9], the Morris-Lecar (ML) model [10], the Chay model [11], and the Smolen and Keizer model [12].

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 [13, 14, 15, 16]. 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 [17]. 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 [18, 19, 20, 21] and network of cells [22, 23, 24, 25] 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 [26] investigated how the activity of the ion channels are regulated by anaesthetics. The three-dimensional ML model was used by Marreiros et al [27] for modelling dynamics in neuronal populations using a statistical approach. Also, González-Miranda [28] investigated pacemaker dynamics in ML model using the three-dimensional model. Gall and Zhou [29] considered four-dimensional ML model by including the second inward sodium Na^+ current.

In recent years, experimental and computational analyses have suggested that sodium Na^+ currents are relevant in the depolarisation of action potential in some muscle cells [30, 31, 32]. Motivated by these results, in this present paper we propose to investigate the influence of including sodium inward currents on variation of membrane voltage of a single excitable cell. Bifurcation analysis is often used to investigate the mode of transition of electrical activities of excitable cell. It helps us to identify the key parameters that cause changes in the dynamical behaviour qualitatively [33]. A lot of studies on bifurcation analyses have been carried out on the two-dimensional [18, 34, 35, 36] and three-dimensional ML models [28], however, to our knowledge apart from the work of [29] there appears no work in the literature that has considered the bifurcation analysis of the four-dimensional ML model. The external current is considered as the bifurcation parameter by [29] whereas in this present paper we focus on the maximum conductances of ion currents as the bifurcation parameters. As a consequence, we show some

additional results that are not present in the existing results of ML model.

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

2. Model Equation

The modified ML model consists of ODEs [29]

$$C \frac{dV}{dt} = I_{\text{ext}} - I_L - I_{\text{Ca}} - I_K - I_{\text{Na}}, \quad (1)$$

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

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

$$\frac{dw}{dt} = \lambda_w(V)(w_{\infty}(V) - w), \quad (4)$$

where V is the membrane potential, m , n and w are the fraction of open calcium, potassium and sodium channels, respectively. The ionic currents in (1) are defined as

$$\begin{aligned} I_L &= g_L(V - v_L), \quad I_{\text{Ca}} = g_{\text{Ca}}m(V - v_{\text{Ca}}), \\ I_K &= g_Kn(V - v_K), \quad I_{\text{Na}} = g_{\text{Na}}w(V - v_{\text{Na}}), \end{aligned} \quad (5)$$

where g_L , g_{Ca} , g_K , and g_{Na} are the maximum conductances of the leak, calcium, potassium, and sodium channels, respectively. Also v_L , v_{Ca} , v_K , and v_{Na} are the Nerst reversal potentials of the leak, calcium, potassium, and sodium channels, respectively, while I_{ext} is the external current and C is the membrane capacitance. 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. 1. The fraction of open calcium, potassium and sodium channels at steady

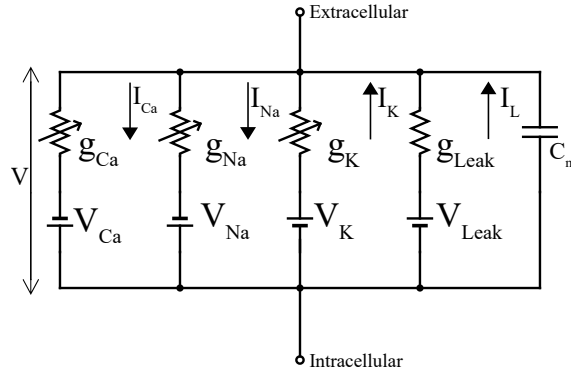


Fig. 1: Equivalent circuit representation of the cell membrane with four ionic channels.

state, denoted by m_∞ , n_∞ and w_∞ , are defined as

$$\begin{aligned} m_\infty(V) &= 0.5 \left(1 + \tanh \left(\frac{V - \bar{v}_1}{\bar{v}_2} \right) \right), \\ n_\infty(V) &= 0.5 \left(1 + \tanh \left(\frac{V - \bar{v}_3}{\bar{v}_4} \right) \right), \\ w_\infty(V) &= 0.5 \left(1 + \tanh \left(\frac{V - \bar{v}_5}{\bar{v}_6} \right) \right). \end{aligned}$$

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

$$\begin{aligned} \lambda_m(V) &= \psi_m \cosh \left(\frac{V - \bar{v}_1}{2\bar{v}_2} \right), \\ \lambda_n(V) &= \psi_n \cosh \left(\frac{V - \bar{v}_3}{2\bar{v}_4} \right), \\ \lambda_w(V) &= \psi_w \cosh \left(\frac{V - \bar{v}_5}{2\bar{v}_6} \right). \end{aligned}$$

Unless otherwise stated, parameter values are as listed in [29]: $C = 1$, $I_{\text{ext}} = 50$, $g_L = 2$, $v_L = -50$, $g_{\text{Ca}} = 4$, $v_{\text{Ca}} = 100$, $g_K = 8$, $v_K = -70$, $g_{\text{Na}} = 2$, $v_{\text{Na}} = 55$, $v_1 = -1$, $v_2 = 15$, $v_3 = 10$, $v_4 = 14.5$, $v_5 = 5$, $v_6 = 15$, $\psi_m = 1$, $\psi_n = 0.0667$, $\psi_w = 0.033$.

2.1. Changes to Excitable Dynamics as a Parameter is Varied

As seen in previous studies [28, 18], 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 (1)–(4). 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 [37]. The dynamics of the membrane potential V upon varying Na^+ current conductance g_{Na} is shown in Fig. 2. For the range of values of g_{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 $g_{\text{Na}} = -20$ are shown in Figs. 2(a) and 2(b), respectively. Upon increasing g_{Na} , periodic oscillations of action potentials are observed in the system, see Fig. 2(c). The periodic oscillations correspond to a closed loop in the phase space, see Fig. 2(d). 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(e) and 2(f). 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 (1)–(4) change as parameter values is varied.

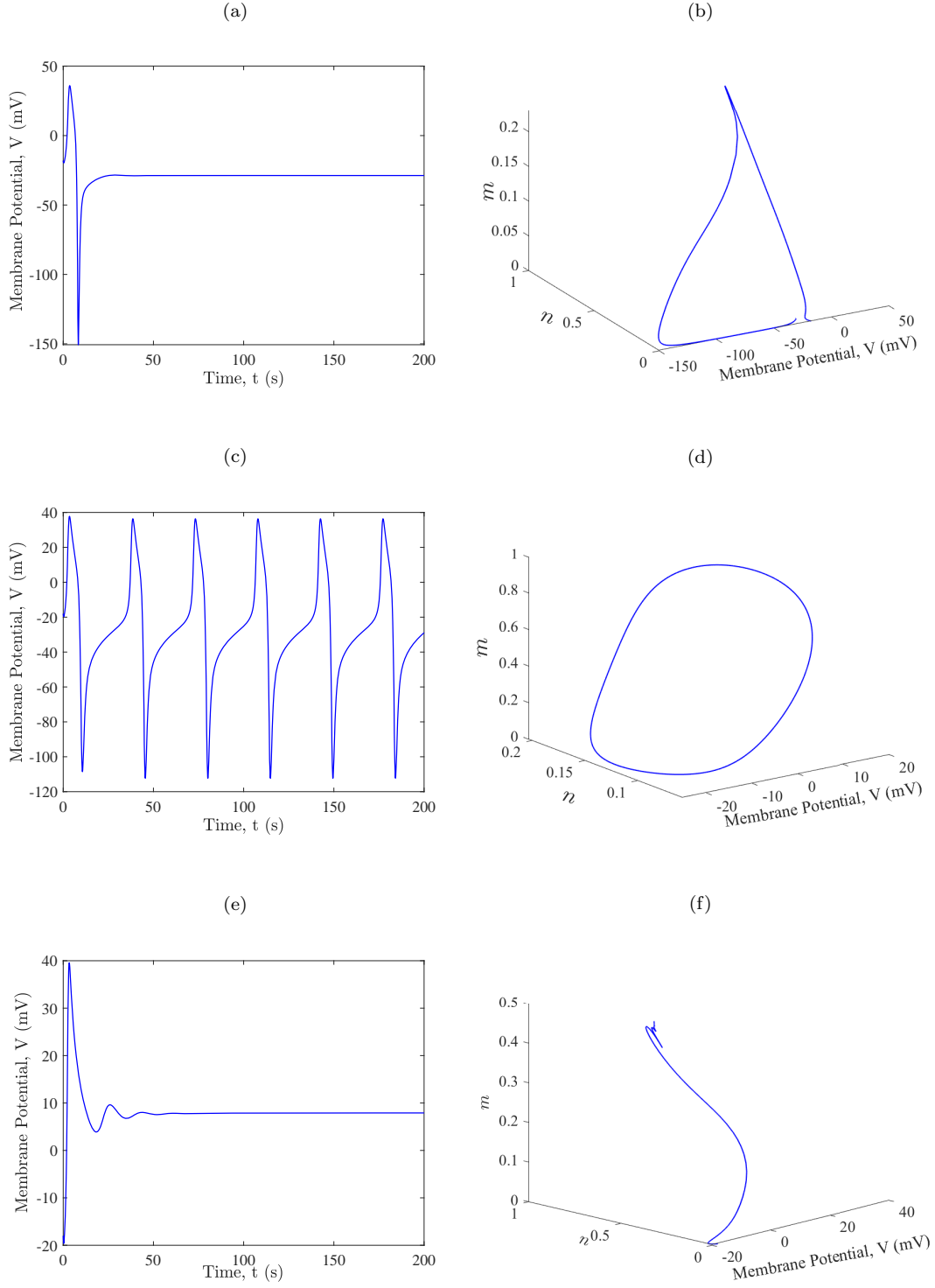


Fig. 2: Numerical simulations of the membrane potential V for (a) $g_{Na} = -20$; (c) $g_{Na} = -10$; (e) $g_{Na} = 1.8$. Their corresponding phase space are (b), (d) and (f), respectively.

3. Numerical Bifurcation Analysis

With the aid of bifurcation analysis, we examine the dynamical behaviour of model (1)–(4) 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 1.

Table 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

3.1. Influence of g_{Na}

Here, we vary g_{Na} to explore the effects of Na^+ current on the dynamical behaviour of model (1)–(4). Fig. 3 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(a), 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(b). 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 [38, 39]. Table 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. 4. 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.

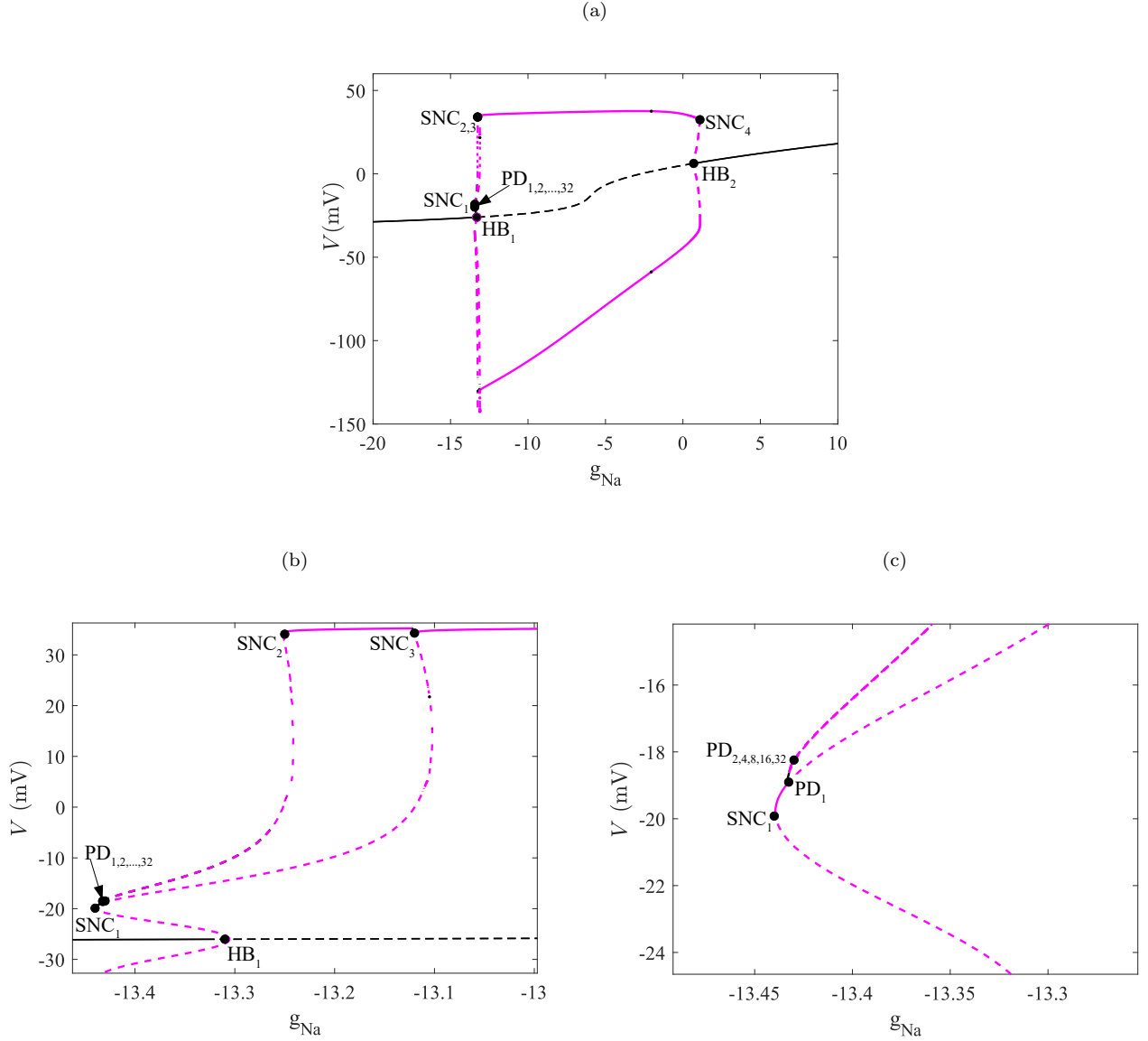


Fig. 3: (a) Bifurcation diagram of the membrane potential V with g_{Na} as bifurcation parameter. The remaining parameter values are fixed as in Sec. 2. (b)-(c) are enlargements of (a). Continuous [dashed] curves correspond to stable [unstable] solutions. Black [magenta] curves correspond to equilibria [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 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

3.2. Influence of g_K and g_{Ca}

Fig. 5(a) 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 values and high values of g_K , the equilibrium is stable. Increasing g_K , the system loses stability through a subcritical Hopf bifurcation HB₁ 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 SNC₁ at $g_K \approx 9.345$. As g_K increases further, the stable limit cycle changes stability in another saddle node bifurcation of cycles SNC₂ at $g_K \approx 46.598$. The unstable limit cycle ends in another subcritical Hopf bifurcation HB₂ 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 $42.583 \leq g_K \leq 46.598$.

Next, we vary the value of the parameter g_{Ca} . Fig. 5(b) 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 HB₁ 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 SNC₁ at $g_{Ca} \approx 1.5974$. As g_{Ca} increases further, the stable limit cycle loses stability in another saddle-node bifurcation SNC₂ at $g_{Ca} \approx 3.2579$ and the unstable limit cycle ends in a subcritical Hopf bifurcation HB₂ 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_{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

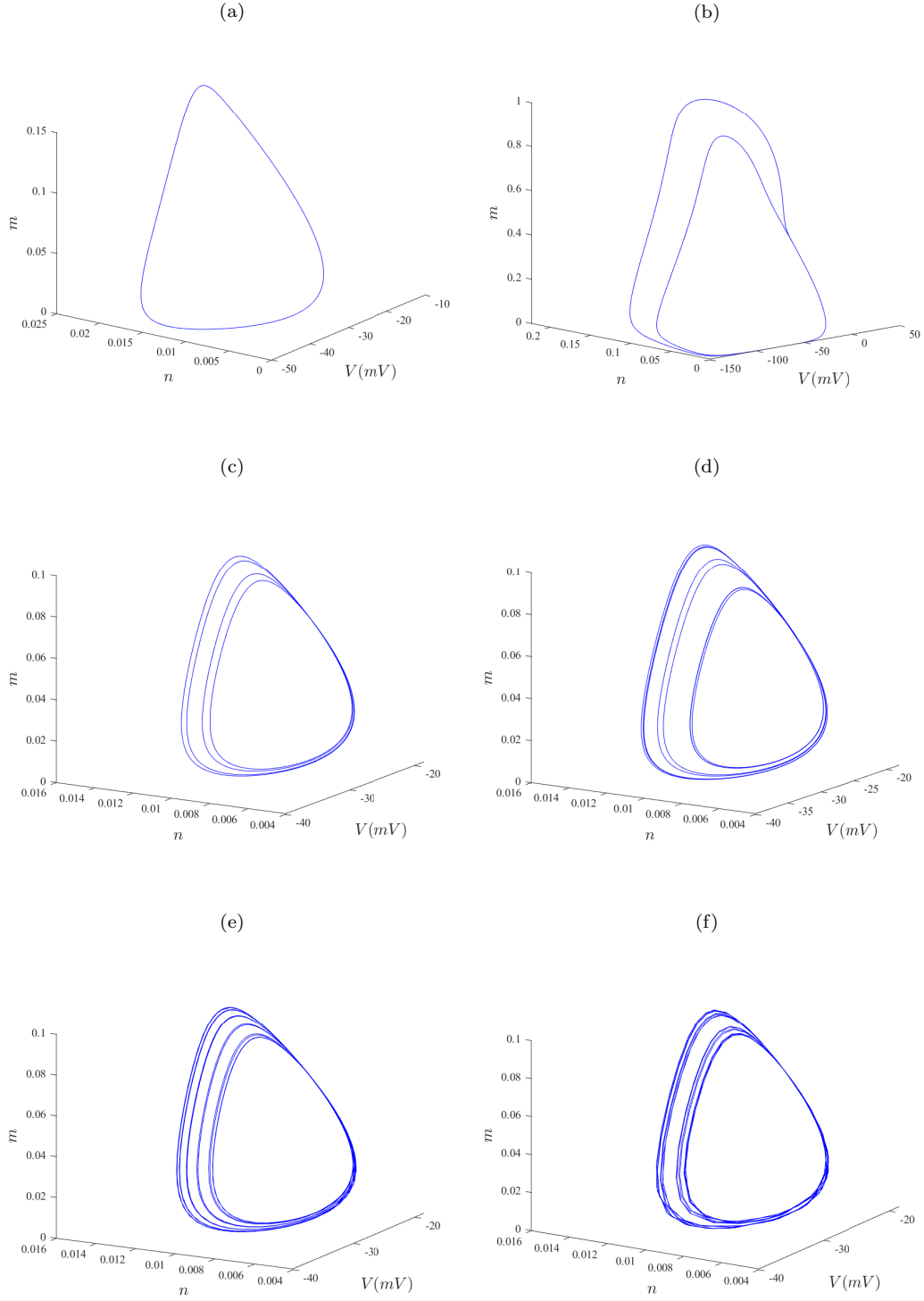


Fig. 4: Phase-space of (1)–(4) showing the cascade of period-doubling bifurcations. (a) Period-1 (b) Period-2 (c) Period-4 (d) Period-8 (e) Period-16 (f) Period-32, respectively.

consider the effects of I_{ext} using two parameter sets. For set I, the parameter values are as listed in Section 2. Fig. 6(a) is a bifurcation diagram of the membrane potential V with the applied current I_{ext}

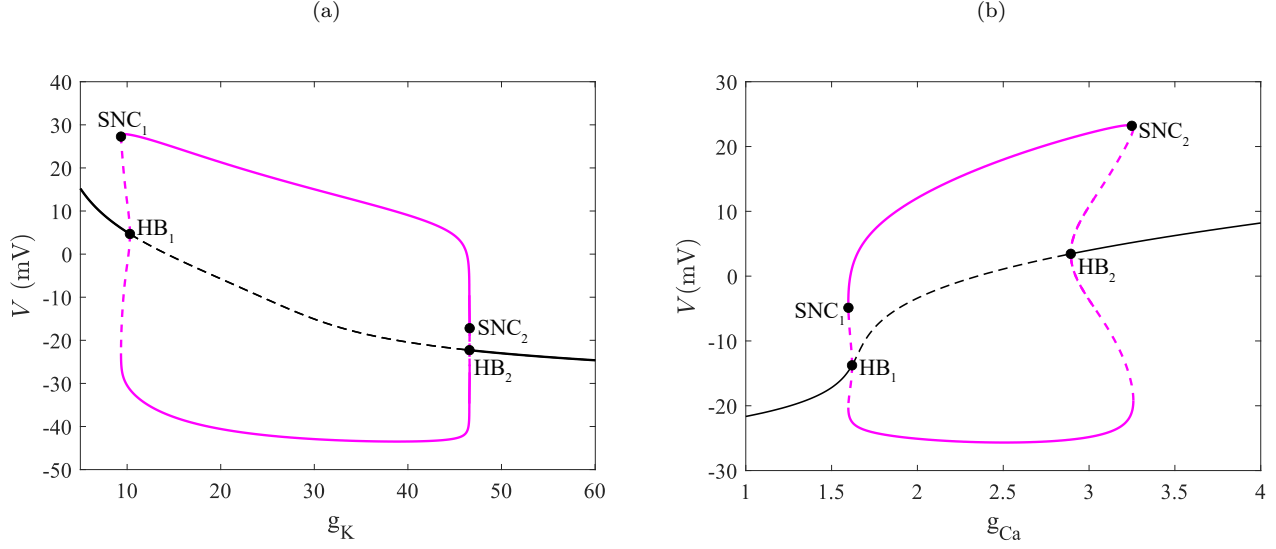


Fig. 5: Bifurcation diagrams of the membrane potential V with (a) g_K (b) g_{Ca} as the bifurcation parameters and other parameters are fixed as in Sec. 2. The labels and other conventions are as in Fig. 3.

as a bifurcation parameter, other parameters fixed. For very low value of I_{ext} , a unique stable equilibrium point exists. Upon increasing I_{ext} , the system changes stability through a saddle node bifurcation SN_1 at $I_{ext} \approx 30.52$ and the unstable branch fold back via another saddle node bifurcation SN_2 at $I_{ext} \approx -39.57$. Between the two SN bifurcations, the system has three equilibria: one stable (lower branch) and two unstable (upper and middle branch), see Fig. 6(a). The upper unstable branch changes stability at a subcritical Hopf bifurcation HB at $I_{ext} \approx 6.656$ before the system returns to a rest state as I_{ext} increases. The unstable limit cycle emanated from HB fold back and changes to a stable limit cycle through a saddle node bifurcation of cycles SNC_1 at $I_{ext} \approx 26.84$. The limit cycle loses stability at another SNC_2 at $I_{ext} \approx 22.99$ before it terminates at $I_{ext} \approx 23.79$.

For set II, $v_6 = 3$ while other parameters are fixed as in Section 2. A bifurcation diagram of the membrane potential V with I_{ext} as bifurcation parameter is shown in Fig. 7(a). For $I_{ext} < -8.7715$, there exists a unique stable equilibrium point. Upon increasing I_{ext} , the system loses stability through a subcritical Hopf bifurcation HB_1 at $I_{ext} \approx 33.29650$. The unstable limit cycle emanated from HB_1 ends in an homoclinic bifurcation HC_1 at $I_{ext} \approx 33.2911$, see Fig. 7(b). The curve of the homoclinic orbit is shown in Fig. 8a. Increasing I_{ext} slightly there appears a saddle-node bifurcation SN_1 at $I_{ext} \approx 33.2026$, the unstable branch fold back at another saddle-node bifurcation SN_2 at $I_{ext} \approx -8.7715$.

As I_{ext} increases further, the system passes through another saddle node bifurcation SN_3 at $I_{ext} \approx 0.8353$. For $I_{ext} \in [SN_2, SN_3]$, there exist three equilibria; one stable and two unstable. The branch of SN_3 bifurcation folds at another saddle-node bifurcation SN_4 at $I_{ext} \approx -1.7961$, and the unstable upper

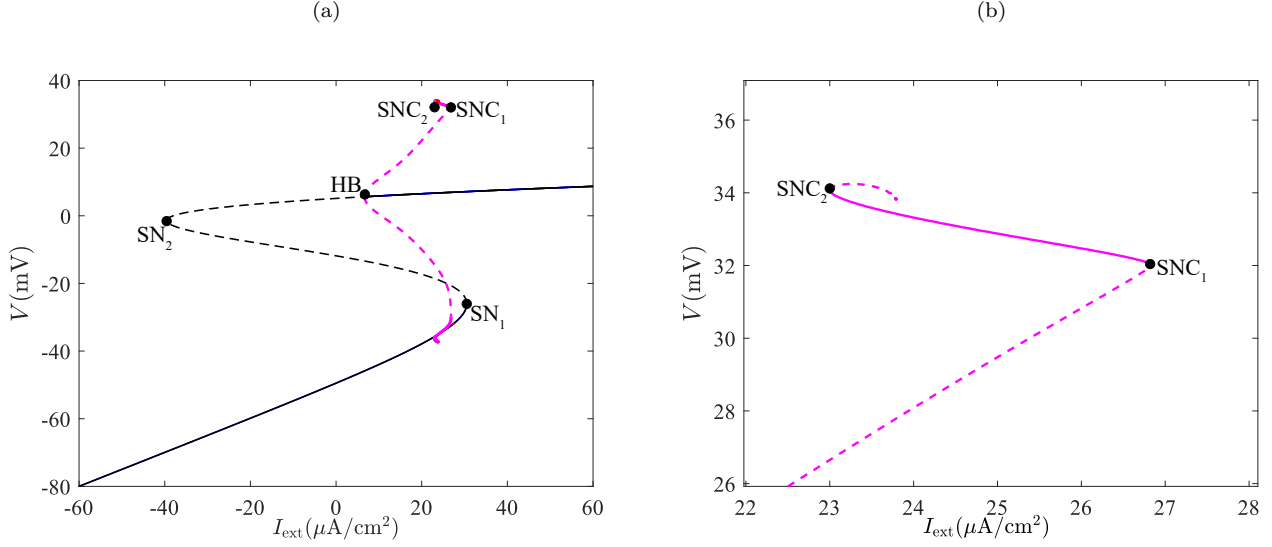


Fig. 6: (a) Bifurcation diagram of the membrane potential V with I_{ext} as the bifurcation parameter. and other parameters are fixed as in Sec. 2. The labels and other conventions are as in Fig. 3.

branch becomes stable in another subcritical Hopf bifurcation 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 SN_1 , the system has a unique stable equilibrium.

The unstable limit cycle generated at the Hopf bifurcation HB_2 fold back at $I_{\text{ext}} \approx 10.80$ and slightly after the fold point appears a period-doubling bifurcation PD_1 at $I_{\text{ext}} \approx 10.77$. At PD_1 , the limit cycle bifurcates into unstable double-period and unstable limit cycles, and they both end in an homoclinic bifurcation, see Fig. 7(c). The curve of the homoclinic orbit is shown in Fig. 8(b). Continuation from the period-doubling PD_1 results in period-doubling bifurcation PD_2 , subsequently, the PD_2 results in period-doubling bifurcation PD_4 . Table 3 shows the parameter values for the period-doubling and homoclinic bifurcations and their corresponding periods as I_{ext} is varied. The projections of periodic trajectories for period-1, 2, 4 onto (V, n, m) phase space are shown in Fig. 9.

3.4. Two Parameter Bifurcation Analysis

In this section we perform two parameter bifurcation analysis of (1)–(4) in (I_{ext}, g_K) plane. The bifurcation diagram shown in Fig. 10 is produced via numerical continuation software MATCONT [40]. The description for the codimension-2 bifurcations are explained in Table. 4. Fig. 10 is divided into regions with respect to different types of dynamical behaviour and we have assigned each region a number, see Table 5. In the remainder of this section we describe the dynamics of model (1)–(4) as I_{ext} and g_K are varied.

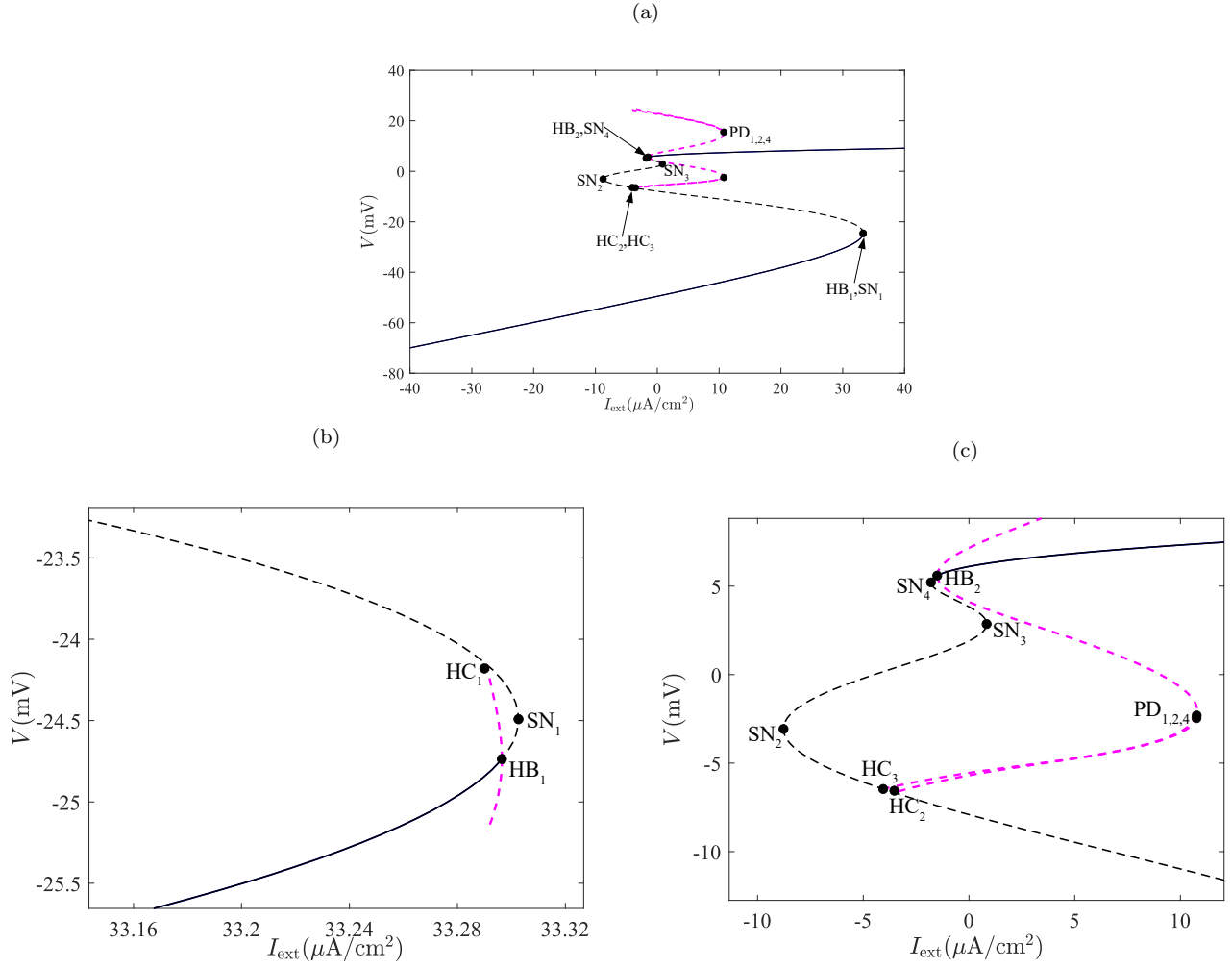


Fig. 7: (a) Bifurcation diagram of membrane potential V with I_{ext} as a bifurcation parameter. (b)–(c) are enlargements of (a). and other parameters are fixed as in Sec. 2. The labels and other conventions are as in Fig. 3.

Table 3: Summary of the parameter values and period of period doubling and homoclinic bifurcations that arise as I_{ext} is varied.

Bifurcation point	I_{ext}	Period
PD ₁	10.7705	33.5585
PD ₂	10.7584	67.1396
PD ₄	10.7555	134.353
HC ₁	33.2911	2.61499E+08
HC ₂	-4.05553	3.95045E+09

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. 10 there are period solutions in region II. A codimension-1 bifurcation diagram along

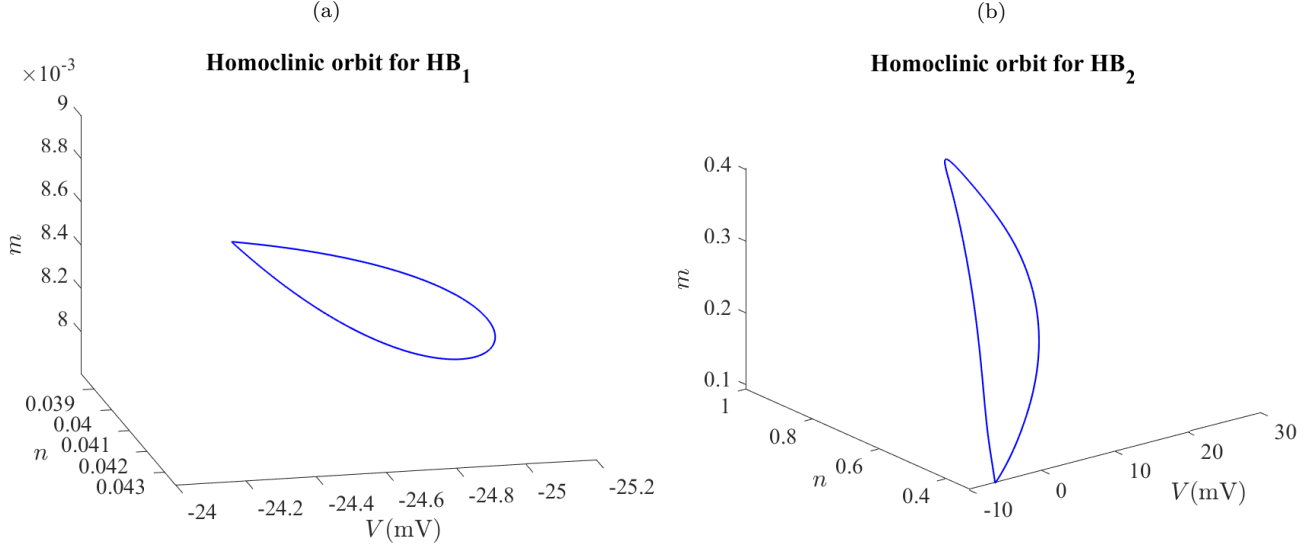


Fig. 8: The curves of homoclinic orbits of the periodic oscillation emanated at (a) HB₁; (b) HB₂.

Table 4: Abbreviations of codimension-two bifurcations.

Bifurcation	Abbreviation
Cusp bifurcation	CP _{<i>i</i>} <i>i</i> = 1, 2, 3
Bogdanov-Takens bifurcation	BT _{<i>i</i>} <i>i</i> = 1, 2
Generalized Hopf bifurcation	GH _{<i>i</i>} <i>i</i> = 1, 2, 3
Zero-Hopf bifurcation	ZH
Generalised Period Doubling bifurcation	GPD _{<i>i</i>} <i>i</i> = 1, 2
1:2 Resonance	R2
Flip-flop bifurcation	LPPD

slice l_1 for which $g_K = 60$ is shown in Fig. 11(a). The stable equilibrium solution loses stability through a Hopf bifurcation HB₂ as I_{ext} is varied. A stable limit cycle emanated from HB₂ ends in another Hopf bifurcation HB₁ before the equilibrium regains stability via HB₁. Here the system passes through regions I→II→I. As the value of g_K decreases, there appears a generalised Hopf bifurcation, denoted GH₁, 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 to subcritical SubHB [33]. Below GH₁, there are two Hopf bifurcations, a subcritical and a supercritical. Fig. 11(b) is a bifurcation diagram along slice l_2 in Fig. 10 for which $g_K = 26$. The system passes through regions I→II→I as in the previous case (slice l_1) except that the stable equilibrium solution in region I loses stability through a subcritical Hopf bifurcation HB₂. An unstable limit cycle

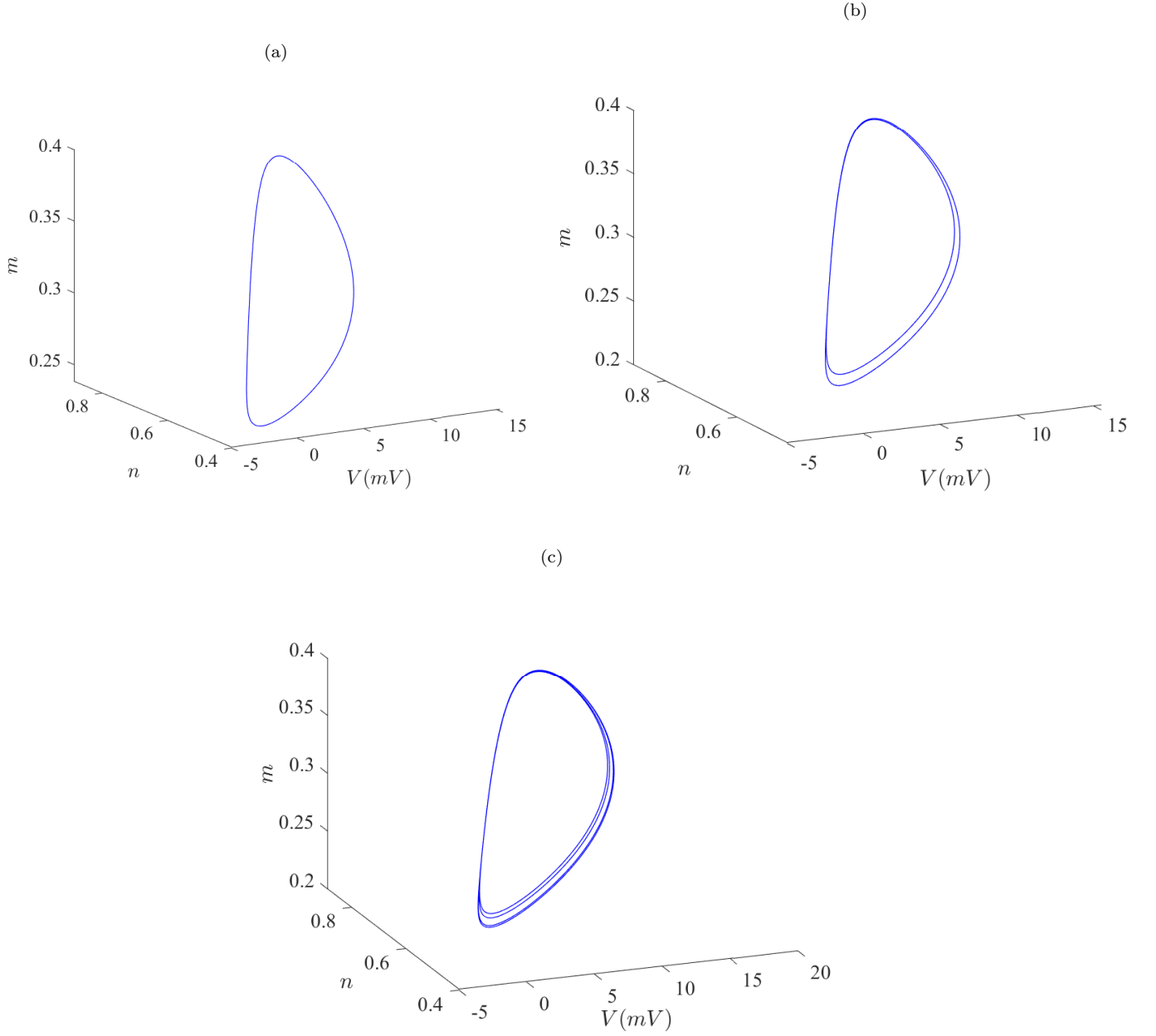


Fig. 9: Phase-space of (1)–(4) showing the period-doubling bifurcations in response to variation of I_{ext} . (a) Period-1 (b) Period-2 (c) Period-4, respectively.

emanated from HB_2 changes stability via a saddle-node bifurcation of limit cycles (SNC), the stable limit cycle ends in a supercritical Hopf bifurcation HB_1 then to the left of HB_1 the equilibrium solution regains stability.

Upon further decrease in the value of g_K , the loci of saddle-node bifurcations SN_1 and SN_2 collide and annihilate in a cusp bifurcation CP_1 at $g_K \approx 18.1715$. As g_K decreases, a 1:2 resonance bifurcation $R2$ and two generalised period-doubling bifurcations GPD_1 and GPD_2 appear on the locus of period doubling

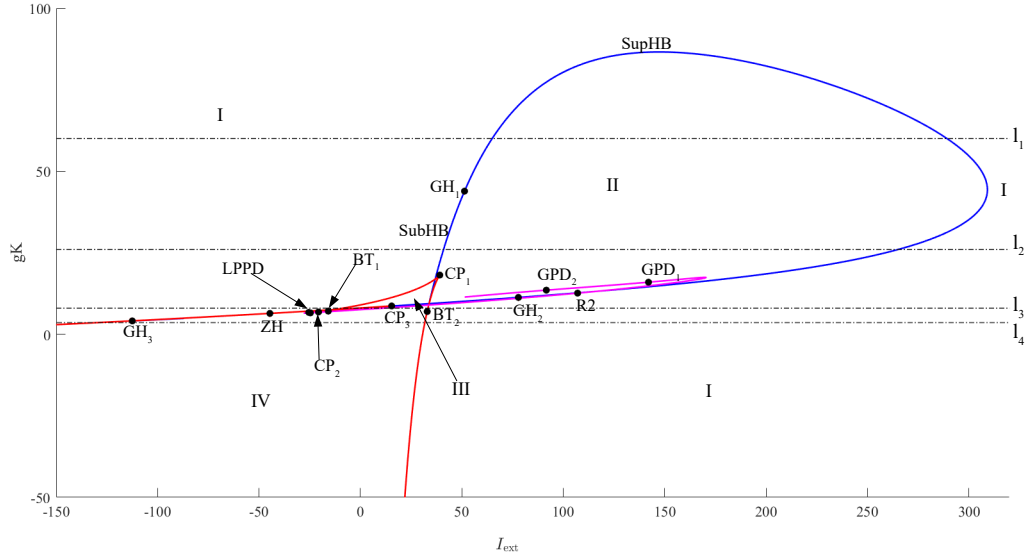


Fig. 10: Two parameter bifurcation diagram of (1)–(4) in the (I_{ext}, g_K) -plane for parameter set II in Section 3.3 and other parameter values as in Section 2. The values of g_K in l_1 , l_2 , l_3 , l_4 are 60, 26, 8 and 3.5, respectively. The blue, red and magenta curves are the loci of Hopf bifurcation, saddle-node bifurcation, and Period doubling bifurcation. The labels for the codimension-2 bifurcations are explained in Table 4. The invariant sets that exist in each region are listed in Table 5.

Table 5: Summary of the six different combinations of equilibria and limit cycles that arise in Fig.10 and its magnifications, Figs. 12a, 12b, and 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.

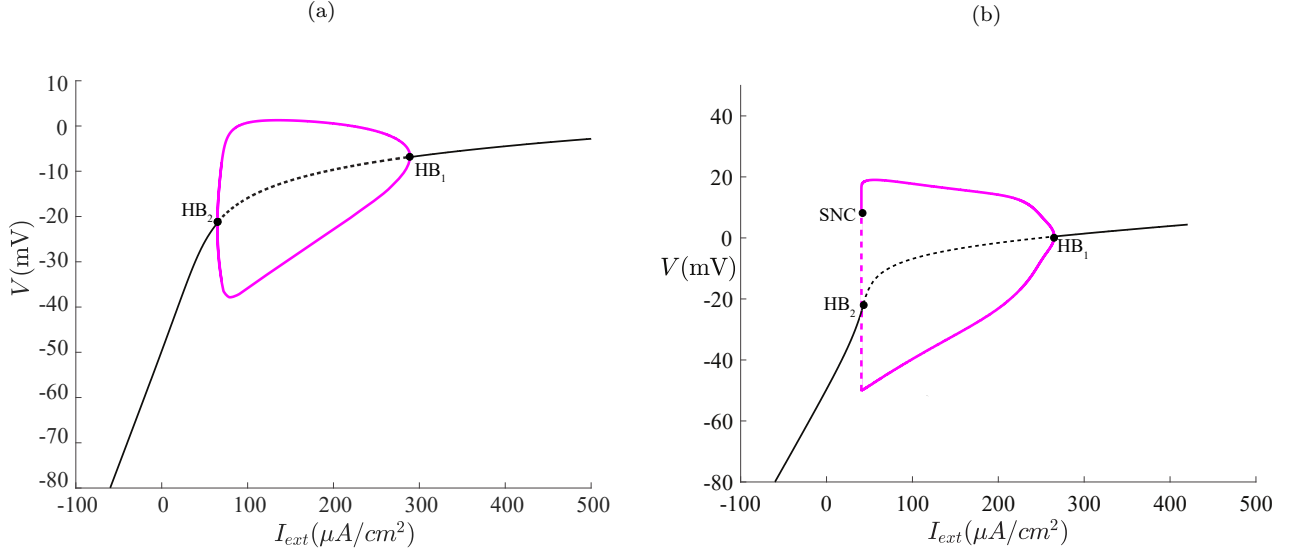


Fig. 11: (a) A codimension-1 bifurcation diagram along line l_1 with $g_K = 60$. (b) A codimension-1 bifurcation diagram along line l_2 with $g_K = 26$. The labels and other conventions are as in Fig. 3.

bifurcation at $g_K \approx 12.624$, 15.982 , and 13.535 , respectively. Also, the loci of saddle-node bifurcations SN_3 and SN_4 collide and annihilate in a cusp bifurcation CP_3 at $g_K \approx 8.6962$ and the supercritical Hopf bifurcation $SupHB$ changes to subcritical Hopf bifurcation in another generalised Hopf bifurcation GH_2 at $g_K \approx 11.3037$, see Fig. 12(a).

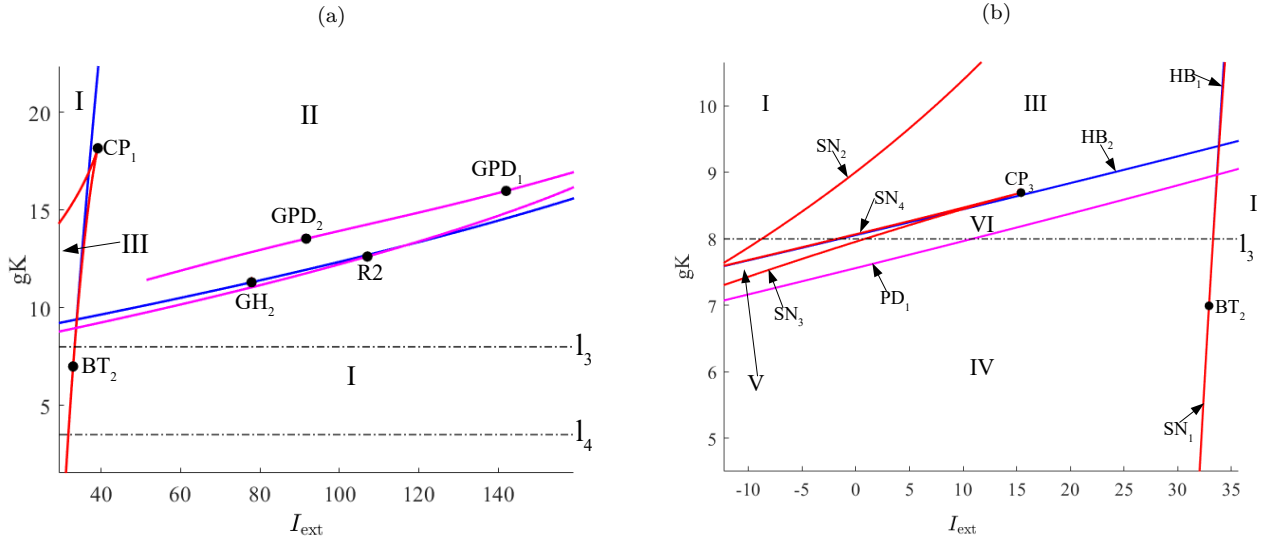


Fig. 12: (a) An enlargement of Fig. 10. (b) An enlargement of Fig. 10 showing line l_3 with $g_K = 8$. The labels and other conventions are as in Fig. 10 and Table. 4.

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. 12(b) along slice l_3 . The corresponding codimension-1 bifurcation diagram for which $g_K = 8$ is shown in Fig. 7(b) and described in Section 3.3. The system passes through

regions $I \rightarrow III \rightarrow V \rightarrow VI \rightarrow IV \rightarrow I$ in Fig. 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_1 and SN_2 at these codimension-2 points. Observed also are the presence of zero-Hopf bifurcation ZH at $g_K \approx 6.4099$, a codimension-2 where the locus of HB_2 intersects 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 in Fig. 13a which is an enlargement of Fig. 13(a). A bifurcation diagram along slice l_4 for which $g_K = 3.5$ is shown in Fig. 13(b). Here the system passes through regions $I \rightarrow IV \rightarrow I$.

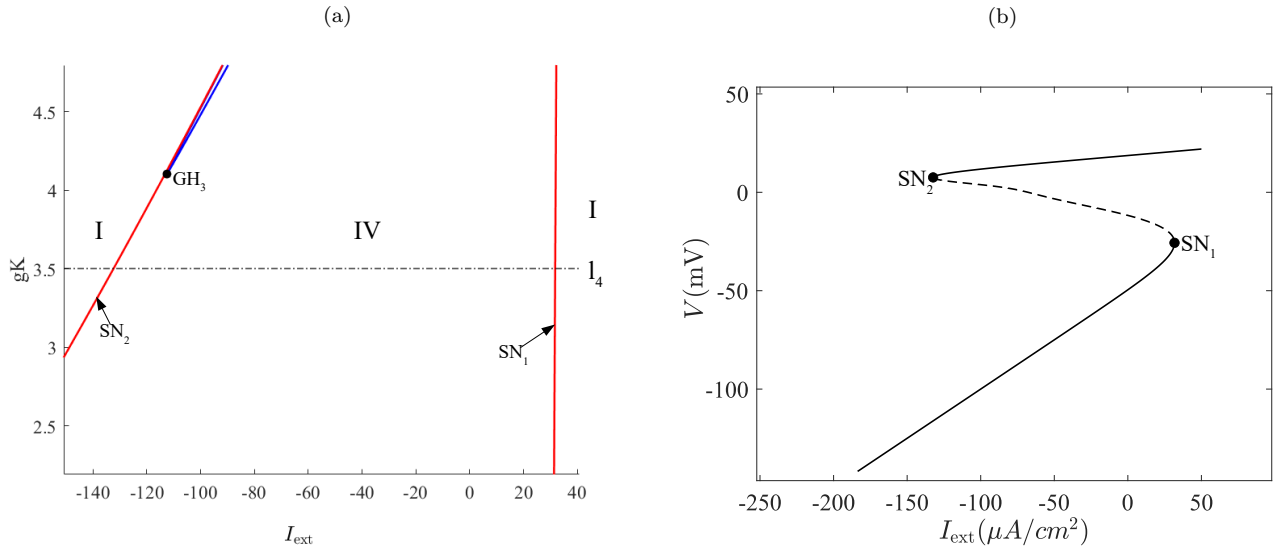


Fig. 13: (a) An enlargement of Fig. 10 showing line l_4 . (b) A codimension-1 bifurcation diagram along line l_4 with $g_K = 3.5$. The labels and other conventions are as in Fig. 10 and Table. 4.

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 [32], where it was 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 [29], 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 $(I_{\text{ext}}, g_{\text{K}})$ -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. [18, 36]. 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 the understanding of various electrical activities in excitable cells where the effect of Na^+ ion can be studied. 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.

Conflict of interest

The authors declare that they have no conflict of interest.

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