MATH 303 Group Project Report

Na-K Model in Neurodynamics

Group members:
Tian-yu Wu, Eric Qu, Samuel Yu, and Yi-fu Wang

Duke Kunshan University
March 2021

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1 Introduction

Neural activity is fundamental to cerebral activity, which in turn is central to the normal functioning of any living body that possesses a neural system. It is important, therefore, that we dedicate to constructing a simplistic but comprehensive model that describes the dynamics behind this important process–the neurodynamics–with as many details as possible.

The physical module of neural activity, the neuron, will be the focus of our inquiry. At rest, neurons maintain an electric potential difference in and out of their membrane, known as the resting potential. Then they receive an electrical stimulus on their dendrite end and should it be sufficiently powerful, it would trigger the cell to enter a process where the potential difference fluctuates. An example of such activity is shown in Figure 1, where a single-peak pulse is generated. In a living body, this would correspond to a single signal.
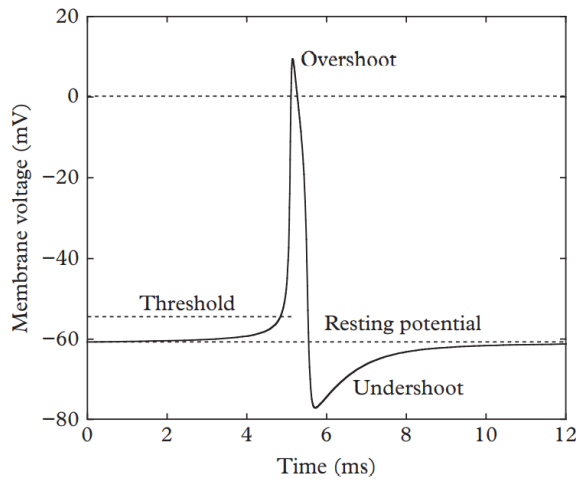

Figure 1: Example of neural activity

The mechanism behind primarily relates to two cations, sodium (Na^+) and potassium (K^+) (Figure 2). At resting potential, membrane proteins called Na-K pumps maintain the potential through net active transport of sodium out of the cell and potassium into the cell, the former being greater in scale, hence that the resting potential is negative. When activated, as shown in the aforementioned figure, voltage-gated Na^+ channels will open, in order to raise the neuron's internal potential up to and above 0, until voltage-gated K^+ channels open to reverse the process, and ad infinitum.
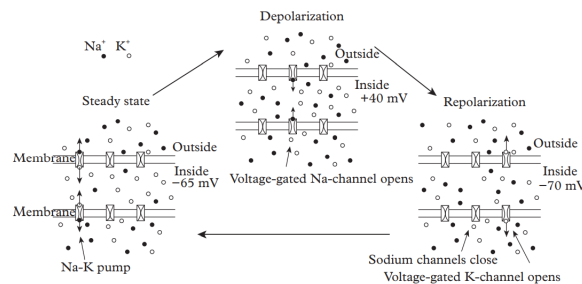

Figure 2: Neural activity cycle

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Such a cycle could lead to the scenario portrayed in Figure 1 under some cases, but in other cases, more intricate and intriguing phenomena might occur, and those would match with varying modes of signaling within an organism. Understanding what defines those various cases would lead us to more properly predict the state of one of the most fundamental actions in biology. With this motive in mind, we set out to investigate a neurodynamical model of ionic flow across neuron membranes, leading to the voltage changes that define neural activity.

In order to carry out a quantitative analysis, some related questions should be set forward. First, asides from membrane voltage, what other parameters and variables are there that could help define the neuron's state? Second, does changing the parameters, particularly those most susceptible to human manipulation, culminate in any bifurcations of the system's dynamics? If so, how would those bifurcations match the neuron's condition?

To answer those questions, we reviewed the literature to find a suitable dynamic model for the neuron. Then, with the use of Mathematica, we apply computational methods to visualize the system's dynamics evolution, as well as how that evolution would alter under various parameter settings. One specific parameter that we focus on is the electric stimulus I, or the bias current, the manipulable external factor that triggers neural action. It shall be discovered that under different I as well as other parameters, we get a series of bifurcations that gives us myriad neural state evolution pathways that fall into two rough categories: approaching a stable point or entering a perpetual cycle. The interchanging of the conditions underlying such pathways reveals much greater details, which are among those that will be covered in the following sections.

2 Literature Review

Neurodynamics, as its name suggests, is the study of dynamical systems in the context of neuroscience. It focuses on the communication between different parts of the nervous system and the relationship between nervous systems and the musculo-skeletal system. The term was firstly introduced in 1989 and has since been further developed over the last 30 years [7]. At present, most neuroscience researches focus upon voltage- and second-messenger-gated currents, and neurodynamics is now seen as a crucial part of injury assessment and treatment [5]. These years has witnessed a moderate amount of positive therapeutic effects through the use of neurodynamical treatment.

Among the research models, the Na-K model stands out when describing the dynamical behavior of neurons, for it is quite simplified. It can be considered as an extension of the Hodgkin–Huxley model [4], where Hodgkin and Huxley describe the voltage-gated currents across the membrane in terms of channel conductance, the equilibrium potential and activation variable first in 1952. Hodgkin and Huxley manage to determine the three major currents carried by the squid axon: voltage-gated persistent K^+ current with four activation gates, voltage-gated transient Na^+ current with three activation gates and one inactivation gate, and Ohmic leak current, I_L, which is carried mostly by Cl^- ions.

One early simplification of the neural dynamics is the Fitzhugh–Nagumo model[2] of the neuron. Under appropriate conditions, it is a simple third-order limit-cycle oscillator like the van der Pol oscillator[10]. The Fitzhugh–Nagumo model has only two dynamical variables: the membrane potential V and the K^+ activation variable n that is proportional to the number of activated membrane channels, which is the same choice in the Na-K model. Qualitatively, this model succeeds in capturing the trends in the dynamics of neuron potentials, but it is lacking in terms of describing concrete details.

When considering a similar Na-K model to describe the neurodynamics, modeling in one dimension is worth consideration[5]. Such a one-dimensional model can be regarded as a reduction of the Hodgkin–Huxley model when all transmembrane conductance has fast kinetics. One example of such a system is the space-clamped membrane having the Ohmic leak current. In this model, it possesses the main concepts of the dynamical system theory: equilibrium, stability, attractor, phase portrait, and bifurcation.

The fundamentals for the Na-K model are introduced in the book by Nolte[8], where he described the formulae for the dynamical system in terms of time derivatives of the membrane potential and the potassium activation variable. He also gave qualitative descriptions of the bistability and bifurcation properties that ensue from this model, without much quantitative detail. In order to conduct quantitative analysis, we have gathered empirical data from more previous works, to assign values to the equation parameters, such as the resting potentials of sodium[1], and the electrical capacitance of neuronal membranes[3].

3 Methodology

The model is described as follows:

$$C\dot{V} = I - g_L \cdot (V - E_L) - g_{Na} \cdot m_\infty(V)(V - E_{Na}) - g_K n \cdot (V - E_K)$$

$$\dot{n} = \frac{n_\infty(V) - n}{\tau}$$

where

$$m_\infty(V) = 1 \ / \ (1 + \exp(\frac{V_{m_{half}} - V}{k_m}))$$

$$n_\infty(V) = 1 \ / \ (1 + \exp(\frac{V_{n_{half}} - V}{k_n}))$$

With V and n as defined previously, the term $g_L \cdot (V - E_L)$ refers to the leak I_L from channels for ions other than Na^+ and K^+, primarily chlorine. Here, g_L represents the conductance of such channels while E_L is the membrane potential difference for the ion at rest. Similarly, $g_K n \cdot (V - E_K)$ describes the potassium flow current I_K of potassium channels, and $g_{Na} \cdot m_\infty(V)(V - E_{Na})$ describes the sodium flow current I_{Na}. The various g terms are defined the same except the ion they stand for, same with the E terms. m is the same as n except for Na^+. In our model, there is the crucial assumption that Na^+ currents are triggered instantaneously compared to K^+, which has a finite lag time τ. Strictly speaking, τ ought to depend on V, but the extent of this dependence is relatively small, so in this model we treat it as constant. m_∞ and n_∞ are the activation variables when $t \rightarrow \infty$, and for they each have a k term as shown that determines how swift they approach 1 as $V \rightarrow \infty$, as well as a V_{half} that marks 50% activation, known as the threshold.

We could now analyze the planer system of $V \ (mV)$ and n and discover the dynamics of neurons using Mathematica to plot the system's evolution under different parameters. To begin, the solution for the V-nullcline is

$$n = \frac{I - g_L \cdot (V - E_L) - g_{Na} m_\infty(V)(V - E_{Na})}{g_K \cdot (V - E_K)}$$

It typically has the form of a cubic parabola. (Shown in Figure 3)
The solution for the n-nullcline is

$$n = n_\infty(V)$$

which is the steady state of K^+ activation function.

In the case of Figure 3 (low-threshold K^+ current), we could observe that the null-clines divided the phase plane into four regions:

(a) Both V and n increase. Na^+ channel and K^+ channel open. This would lead to a upstroke of the action potential.

(b) V decreases but n increases. Na^+ channel closes but K^+ channel still opens. This leads to a downstroke.

(c) Both V and n decrease. Here Na^+ channel and K^+ channel are both closed. This is when the refractory period happens.

(d) V increases but n decreases. Na^+ channel partial opens and K^+ continues to de-activate, leading to a relative refractory period, then to an excitable period, and possibly to another action potential.
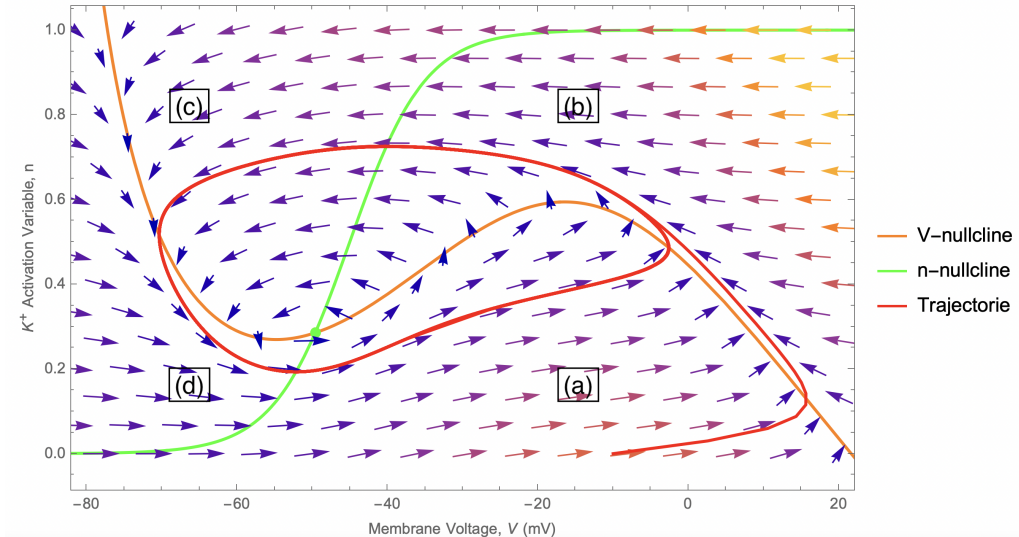
Figure 3: Nullclines of the Na-K model with low-threshold ($V_{n_{half}} = -45mV$) K$^+$ current

3.1 Equilibria

The equilibria of the system are where the nullclines intercept. The system in Figure 3 has only one equilibrium, which is also the resting state. This equilibrium is stable.

But, when we have different settings, we could end up with more than one equilibria. In Figure 4 where the K$^+$ threshold is high, we have three equilibria: A (unstable spiral), B (saddle point), C (stable node). In this case, C is the resting state.
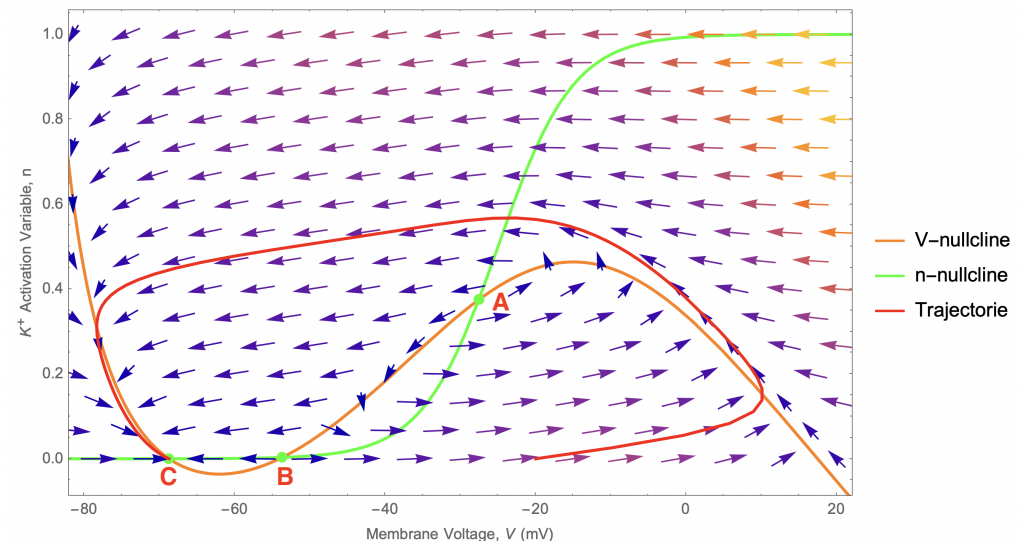

Figure 4: Phase portrait of the Na-K model with high-threshold ($V_{n_{half}} = -25mV$) K$^+$ current

3.2 Bistability

Most neural models are bistable, usually with one stable focus equilibrium corresponding to the resting state and one stable limit cycle attractor corresponding to the repetitive firing state.
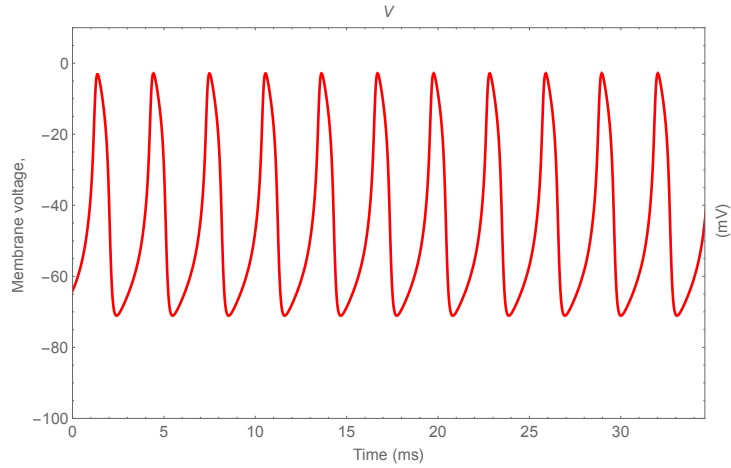
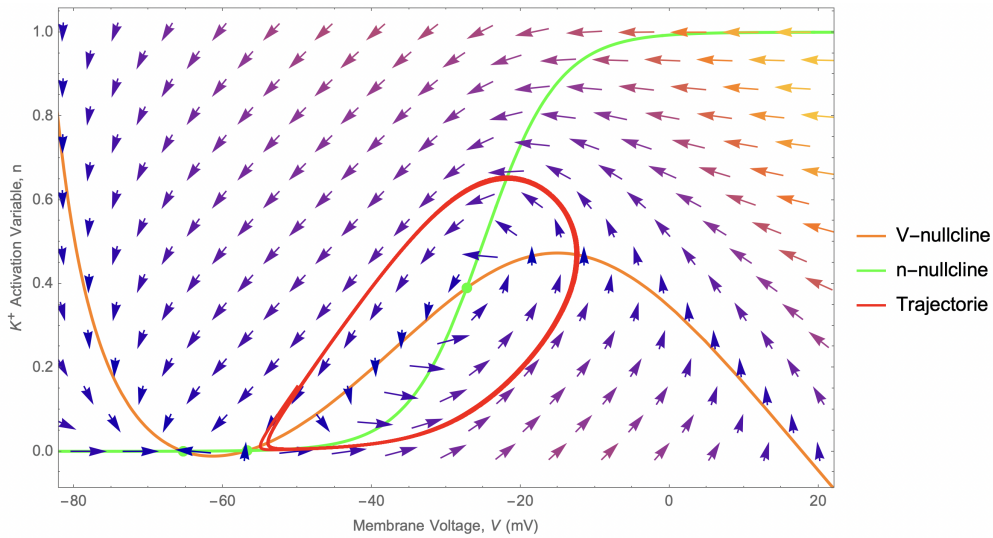Figure 5: Voltage verses time plot in Na-K model with low-threshold K$^+$ current

Figure 6: Phase portrait of the Na-K model with high-threshold and smaller τ

For the system in Figure 6, it is defined not only by a high K$^+$ threshold, but also by a smaller $\tau = 0.152$ compared to the previous case, where $\tau = 1$. The resting state came from the partially activated Na$^+$ and leak channels. The repetitive firing state is caused by the K$^+$ channel deactivating too fast so that the voltage could not return to the sub-threshold range. The voltage of spiking states is shown in Figure 7.

The trajectory in Figure 6 is the approximation of separatrix (it is a homoclinic orbit). The stable manifold is inside the trajectory. If the initial state starts within the trajectory, it would start the stable limit cycle. If it is outside the trajectory, it would end up in the resting state. As in Figure 6, all time units will be in ms.

Through the analysis of the model, we discovered that the Na-K model could undergo multiple types of bifurcations. By numerical simulation with the parameters found in the literature, we summarized the bifurcations in the results section.
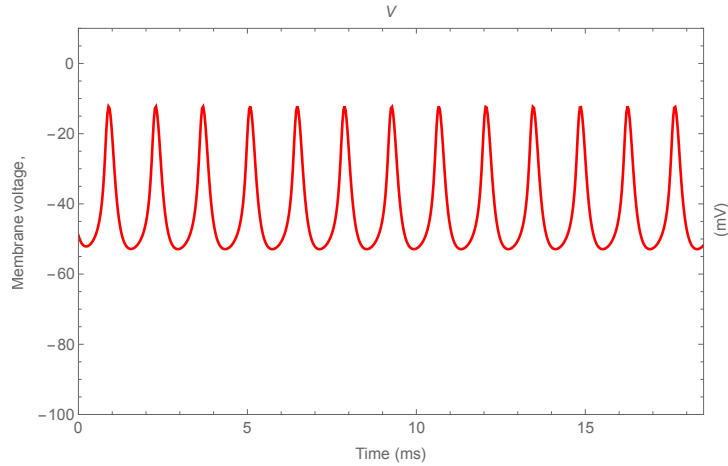
Figure 7: Voltage verses time plot in spiking states

4 Results

4.1 Saddle-Node Bifurcation

Firstly, the system undergoes the saddle-node bifurcation, as we mentioned above. Figure 8 summarized its behavior: when the injected current increases, the saddle and stable node equilibria approach each other, coalesce, and annihilate each other.

We could solve for the required bias current I (the unit of which we take to be μA) of the bifurcation by transforming the equilibrium equation

$$0 = I - g_{\mathrm{L}} \cdot (V - E_{\mathrm{L}}) - g_{\mathrm{Na}} m_{\infty}(V) (V - E_{\mathrm{Na}}) - g_{\mathrm{K}} n_{\infty}(V) (V - E_{\mathrm{K}})$$

to solve for I:

$$I = g_{\mathrm{L}} \cdot (V - E_{\mathrm{L}}) + g_{\mathrm{Na}} m_{\infty}(V) (V - E_{\mathrm{Na}}) + g_{\mathrm{K}} n_{\infty}(V) (V - E_{\mathrm{K}})$$

The solution (Figure 8) is called the bifurcation diagram of saddle-node bifurcation. For all plots, I_{ext} refers to I, the bias current.

But from the simulation, we discovered another type of saddle-node bifurcation. This type is called Saddle-Node bifurcation on Invariant Circle. The bifurcation occurs on an invariant circle, which is defined by "any solution starting on the circle remains on the circle". Before the bifurcation, the invariant circle consists of two trajectories: the longer one start from the saddle and end at the node (drawn in the first subfigure in Figure 9), the shorter one goes the other way along the x-axis, also start from the saddle and end at the node. Both trajectories are heteroclinic (start from one equilibrium and end at another one). When the bifurcation happens, the small trajectory shrinks, and the large heteroclinic trajectory becomes a homoclinic invariant circle. After the bifurcation, the circle becomes a limit cycle.

The change of parameters for these two bifurcations is the time constant τ of the K^+ current. Since the K^+ current has a high threshold, the time constant has little influence on steady state. But it has significant effects in action potential. If the current is fast (Figure 8), it activates during the upstroke, thereby decreasing the amplitude of the action potential, and deactivates during the downstroke, thereby resulting in overshoot and another action potential. In contrast, the slower K+ current (Figure 9) does not have time to deactivate during the downstroke, thereby resulting in undershoot, with V going below the resting state.
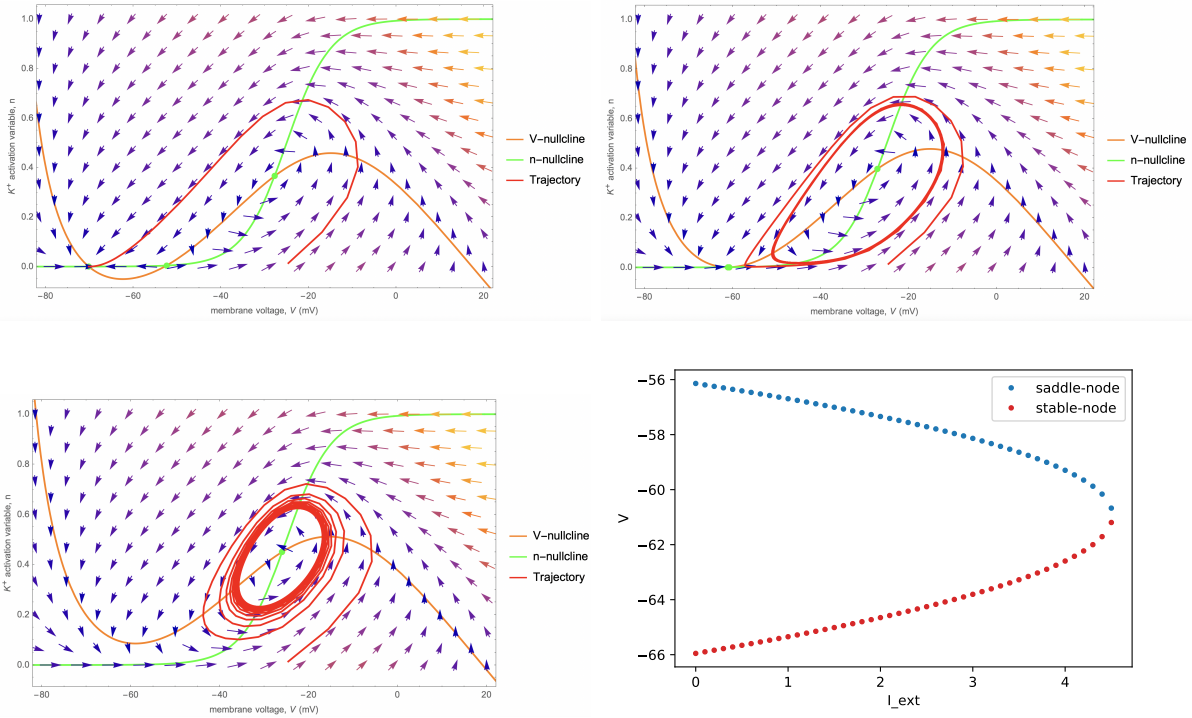
Figure 8: Phase portrait and Bifurcation Diagram of Na-K model with Saddle-Node bifurcation
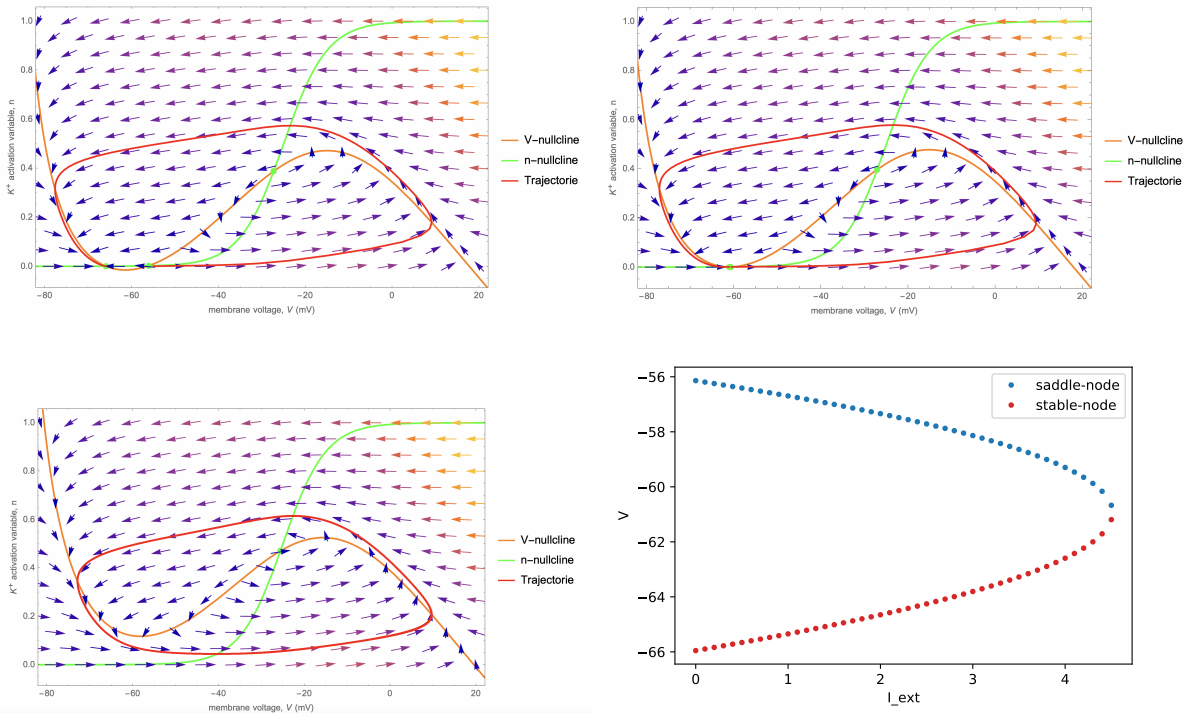

Figure 9: Phase portrait and Bifurcation Diagram of Na-K model with Saddle-Node bifurcation on Invariant Circle

4.2 Andronov-Hopf Bifurcation

Na-K model also undergoes Hopf Bifurcation, both supercritical and subcritical. The Hopf bifurcation happens when the equilibria change from a stable spiral to an

unstable spiral. This is because that as the injected bias current increases, the real part of eigenvalues changed from negative to positive. The supercritical Hopf Bifurcation is that when the bifurcation happens, it gives birth to a stable limit cycle. Also, the amplitude of the limit cycle increases as the injected current increases. The subcritical Hopf Bifurcation is that when the bifurcation happens, an unstable limit cycle vanishes. The phase portrait and Bifurcation Diagram of Supercritical Hopf bifurcation could be found in Figure 10.
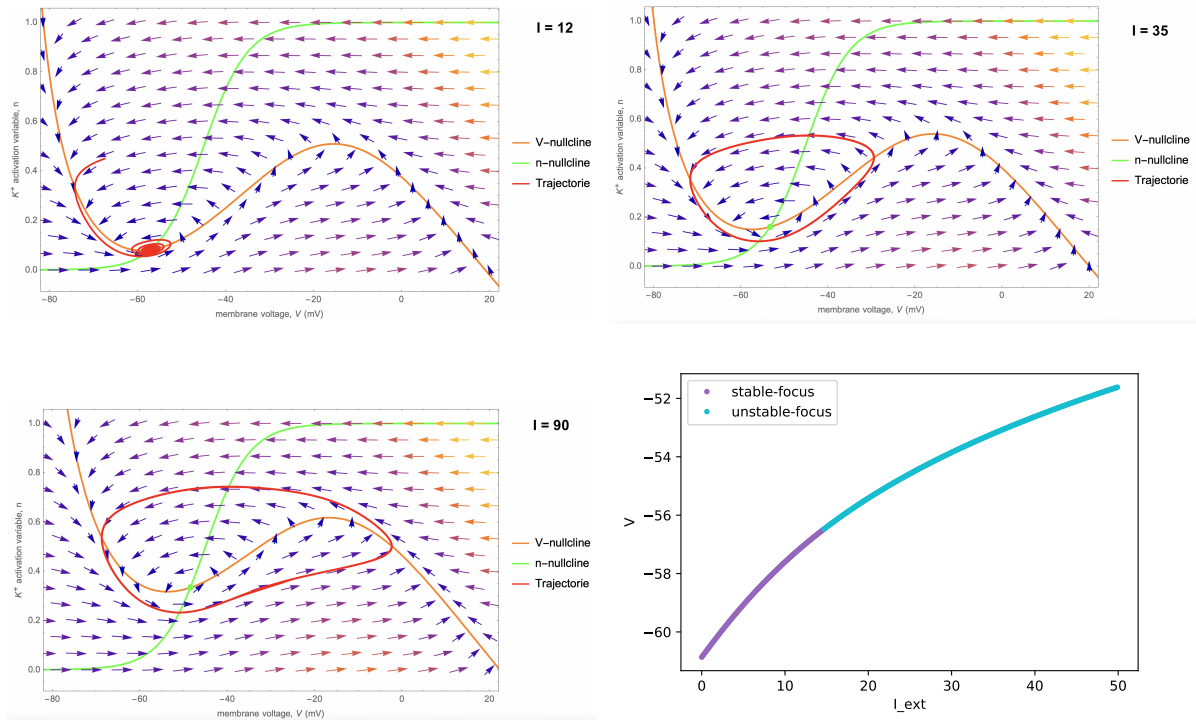

Figure 10: Phase portrait and Bifurcation Diagram of Na-K model with Supercritical Andronov-Hopf bifurcation

When we plot the bifurcation diagram of subcritical Hopf bifurcation, we discovered an interesting phenomenon as we increase the bias current. After the subcritical bifurcation, the model undergoes two saddle-node bifurcations. Details are shown in Figure 11.
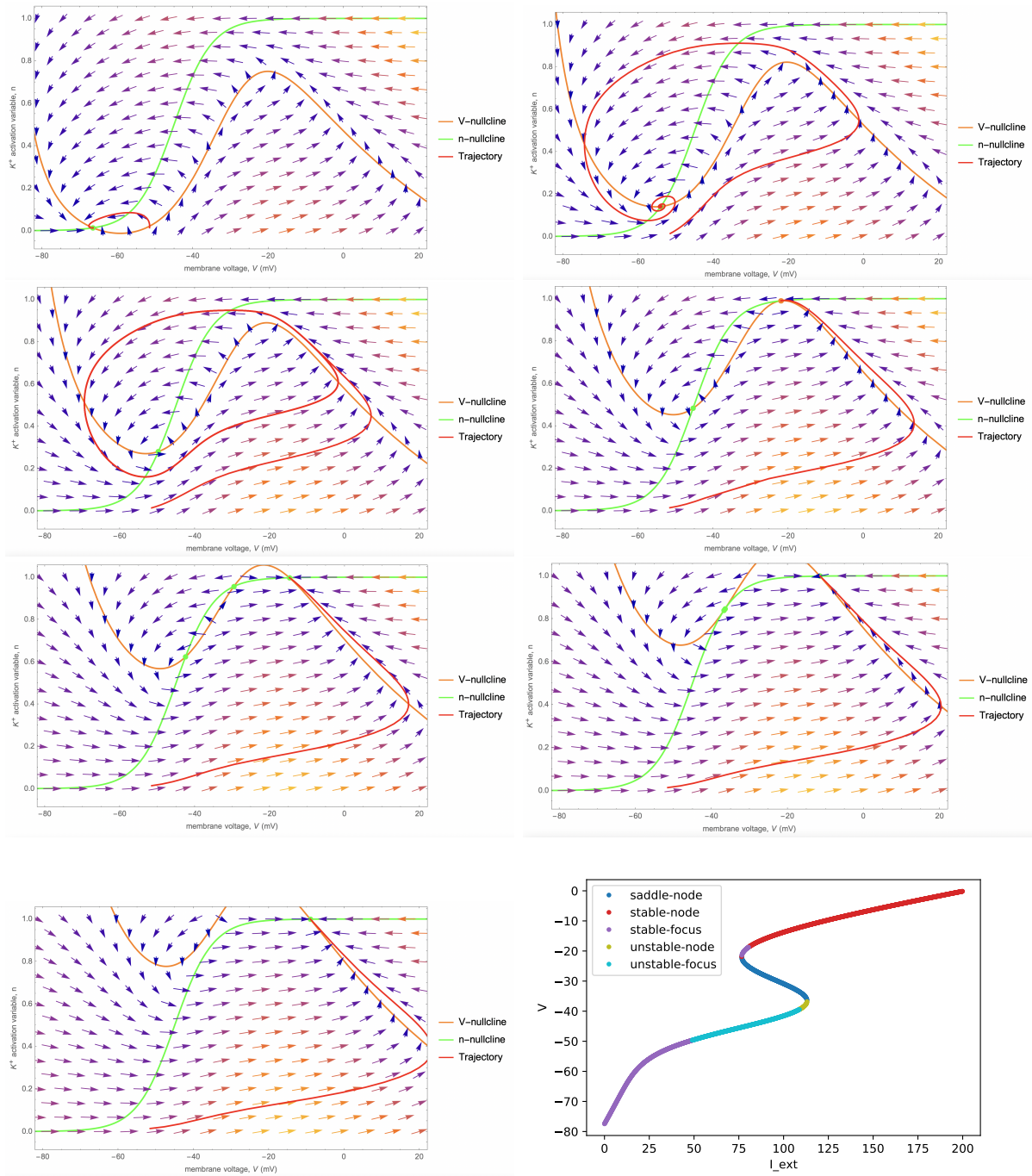
10

Figure 11: Phase portrait and Bifurcation Diagram of Na-K model with Subcritical Andronov-Hopf bifurcation

5   Application and Biological Significance

The research of the Na-K model is considered as one of the most important parts based on dynamical system, in neurodynamics studies. Through behavioral testing, we found that it could capture much subtler behavior of neurons realistically, and could help describe neurons' various functions.

Na-K model can accurately describe the physical processes of ion currents through neuron membranes and the dependence of these currents on membrane potentials, and this method can also be applied in a broader way. At present, many neuroscience studies

deal with voltage- and second-messenger-gated currents, which enables neurodynamics methodology to be an important part of injury assessment and treatment clinically. These years has shown many positive therapeutic results with neurodynamical treatment in clinical practice. So the simulation result of Na-K model, (i.e. those visualizations in the argument above), could help physicians to interpret the result more accurately, and can illustrate physiological explanations for the patients, in order to make it clear about potential abnormal reflexes among the neurons.

In addition, the function of our research in neurons is not limited to help solve human pathology problems, but also beneficial for the development of artificial neural networks. Biological neurons have provided excellent examples of the complexities of neural behavior, but they seem to be too complex as models for artificial neurons in the neuron networks. Therefore, a reasonably simplified model, like the Na-K Model, can genuinely help scientists to construct idealized neuron behavior either computationally or in hardware implementations in the future. This implies that a more reasonable and accurate interpretation of the model is beneficial for the progress of Artificial Intelligence in the future.

6   Conclusion

In our research, we investigated the Na-K model, a neurodynamical model that simplifies the physics of neural electric potential changes to the best extent and is an improvement on past models. We obtained our results through numerical simulation by Mathematica to visualize the phase portrait of when membrane potential and K^+ channel activation variable change as functions of time, tending specifically to the observation of bifurcation phenomena under different parameters, most notably the bias current stimulus, as well as the neurons' on activation threshold for K^+ channels.

The outcomes show that depending on the height of K^+ channel thresholds and bias current intensities, we could have either saddle-node or Andronov-Hopf bifurcations. In the former case, there may exist a limit cycle that surrounds an unstable equilibrium with a high rate of change of K^+ channel activity and all other parameters controlled. This implies that in neurons where these channels react fast, the same signal might lead to a repetitive firing where in others it leads to but a single peak. This discovery is essential for physicians to solve pathology problems by explicitly understanding the potential abnormal reflexes of the neurons. But it is not limited to human problems in this rapidly evolving environment. The study of their behaviors is conducive to develop artificial neural networks, and then promote the development of artificial intelligence in the future.

References

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7 Appendix

Simulation code (Mathematica)

```
Manipulate[
 Show[
  Plot[{(current - bkmrk[[4]] (v - bkmrk[[9]]) -
       bkmrk[[3]] (1/(1 + Exp[(bkmrk[[10]] - v)/bkmrk[[5]]]) (v -
          60)))/(bkmrk[[2]] (v + 90)),
    1/(1 + Exp[(bkmrk[[11]] - v)/bkmrk[[6]]])} , {v, -150, 50},
   Frame -> True,
   FrameLabel -> {Row[{"membrane voltage, ", Style["V", Italic],
      " (mV)"}],
    "\!\(\*SuperscriptBox[\(K\), \(+\)]\) activation variable, n"},
   PlotStyle -> {{Orange, Thick}, {Green, Thick}},
   AxesOrigin -> {-80, -.2},
   MeshFunctions -> {((current - bkmrk[[4]] (v - bkmrk[[9]]) -
          bkmrk[[3]] (1/(1 +
               Exp[(bkmrk[[10]] - v)/bkmrk[[5]]]) (v -
              60)))/(bkmrk[[2]] (v + 90)) -
        1/(1 + Exp[(bkmrk[[11]] - v)/bkmrk[[6]]])) /. v -> # &},
   Mesh -> {{0}}, MeshStyle -> PointSize[Large]],
  VectorPlot[{current - bkmrk[[4]] (x - bkmrk[[9]]) -
     bkmrk[[3]] ( 1/(
       1 + Exp[(bkmrk[[10]] - x)/bkmrk[[5]]])) (x - 60) -
     bkmrk[[2]] y (x + 90), ((1/(
        1 + Exp[(bkmrk[[11]] - x)/bkmrk[[6]]])) - y)/
     bkmrk[[12]]}, {x, -85, 20}, {y, 0, 1}, VectorStyle -> Black],
  ParametricPlot[
   Evaluate[{x[t], y[t]} /.
     NDSolve[{x'[t] ==
         current - bkmrk[[4]] (x[t] - bkmrk[[9]]) -
          bkmrk[[3]] ( 1/(
            1 + Exp[(bkmrk[[10]] - x[t])/bkmrk[[5]]])) (x[t] - 60) -
          bkmrk[[2]] y[t] (x[t] + 90),
        y'[t] == ((1/(1 + Exp[(bkmrk[[11]] - x[t])/bkmrk[[6]]])) -
           y[t])/bkmrk[[12]], x[0] == inv, y[0] == inn}, {x, y}, {t,
        100}, MaxSteps -> 10^10]], {t, 0, 100},
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  ImageSize -> 1.1 {500, 320}],
 Grid[{
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      Appearance ->
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```

```
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        0.5, -78, -30, -45, 1} ->
      "subcritical Andronov-Hopf bifurcation", {14.66, 10, 20, 8,
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    ImageSize -> Tiny, Appearance -> "Labeled"}]}, {"",
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