Electronic Model of glutamate receptors

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Abstract

It has long been known that the spiking dynamics of a neuron can be mimicked by some simple circuit elements (Hodgkin and Huxley, 1990). In this project we propose a charging-discharging neuron whose dynamic can be controlled by two inputs. One input is used to resemble the glutamate release and the other works as a Mg^{2+} like channel blocker. In general the circuit is analogous to the NMDA receptors.

1 Introduction

Neuron models, which is still under intensive study, can be dated back to the seminar work of Hodgkin and Huxley in 1952 (Hodgkin and Huxley, 1952a,b,c). They shown that the spike activity of a neuron can be modeled by a circuit that only have very basic electronic elements. Remarkably, each circuit element, such as the resistor, the capacitor and the voltage source has a biophysical counterpart in the biological neurons. With the fast development of the silicon industry in the past few decades, electronic pioneers, such as Carver Mead, draw their attention to building electronic circuits that can simulate certain neural functions (Mead, 1989) . Experimental studies (Shi et al., 1999) have shown that NMDA receptors significantly contribute to the synaptic plasticity and people (Morris et al., 1990) speculate that it is important for memory and learning. Thus, an electronic circuit that could resemble NMDA receptors can be potentially useful in achieving certain brain functions. In this project, we propose a simple design for NMDA receptors that is modulated by an input that represents glutamate release and a voltage threshold that represents the voltage-gated Mg^{2+} blocker.

2 Methods

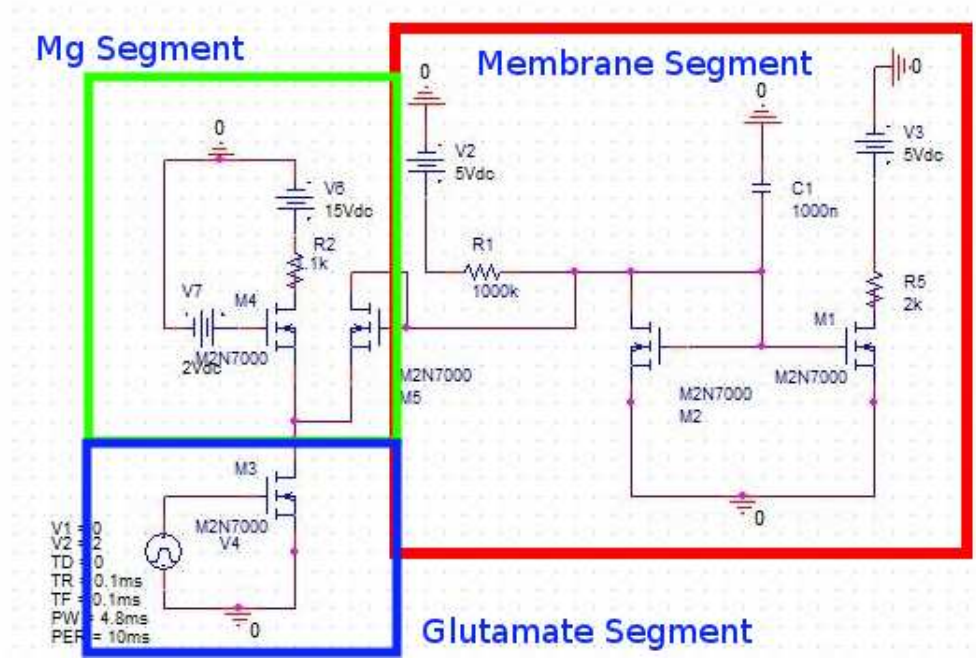

Fig.1 NMDA circuit design.

Synaptic circuit designs have been proposed in the past (Mead, 1989) . In this project, our design is based on the charge-discharge synaptic design that was proposed by Rasche and Douglas (1999) . Shown in figure 1, our circuit could be separated into three parts by its functions. In the membrane segment, a capacitor C1 acts as the cell membrane. Instead of having a negative voltage potential as in neurons, here, our membrane holds a positive potential because this is easier to implement at the circuit level by connecting to a voltage source at V2. The two transistor M1 and M2 act as a current mirror to replicate the current through the membrane. Although this current mirror is not necessary in the context of this project, we expect it to be useful in future large scale designs. This replicated current can be used as a reference for glutamate release at the presynapse when neurons are connected together.

In the Mg^{2+} segment, we used a differential pair as the voltage gate. The current flow through the common source of M4 and M5 depends on the gate voltage of M4 and M5. We note here that the gate voltage of M5 is the membrane voltage. If this voltage is higher than the gate voltage of M4, i.e. the threshold voltage, the drain-source resistance (r_{ds}) of M5 will be negligible and we can think of M5 as a short circuit. On the other hand, if the membrane voltage is lower than the threshold voltage, the resistance between the drain and source of M5 will be very large and M5 could be approximated as an open circuit.

Lastly, for the glutamate segment, we used a periodic square function to represent the glutamate release from the presynapse. Since the square wave is connected to the gate of transistor M3, a high voltage which represents high glutamate concentration, will reduce the drain-source resistance (r_{ds}) of M3. In other words, in the presence of glutamate, M3 is approximately a short circuit. So, there are mainly two stages for the circuit. If the membrane voltage is above the threshold voltage, then since both M5 and M3 could be regarded as short circuits, the membrane will discharge. This could be considered as the open state of the NMDA channel. At certain point of the discharge, the membrane voltage will drop down to a value that is lower than the threshold. Then M5 will become an open circuit as if the NMDA channel is closed. Also, if there is no glutamate signal, M3 has high resistance. Then the membrane can not discharge.

3 Results

To validate our circuit design, we simulated the dynamics of the circuit in software with different threshold voltages.

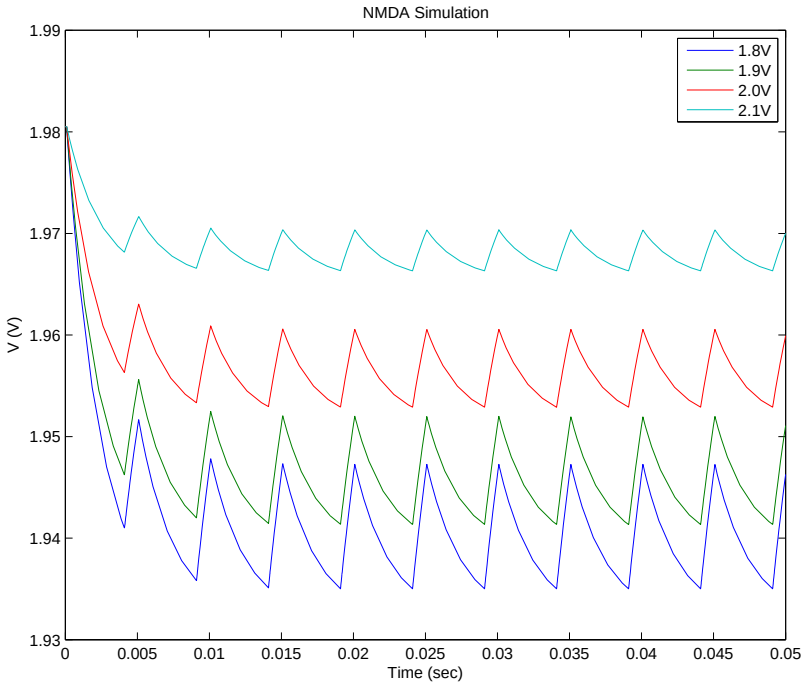

Fig.2 Simulated spike trains with different threshold voltages.

As shown in figure 2, due to the charging and discharging mechanisms mentioned in the method section, the circuit can generate spike trains. Also in this figure, we show that the spike amplitude depends on the threshold voltage.

After putting such circuit into reality, we see similar spike patterns as the simulation results in figure 2. In order to have a more quantitative view about the resemblance of our circuit to the biology NMDA receptors, we studied how the spike changes with respect to two inputs. One is the change of the spikes due to the amount of glutamate release. The other is the variance of the spikes with respect to the threshold voltage. We argue that these two properties are characteristic for NMDA receptors and are critical for describing the dynamics of the NMDA receptors. Also real physiology experiments have been done on similar tasks and can be used as a reference to evaluate our design (Jahr and Stevens, 1990a; Popescu et al., 2004) .

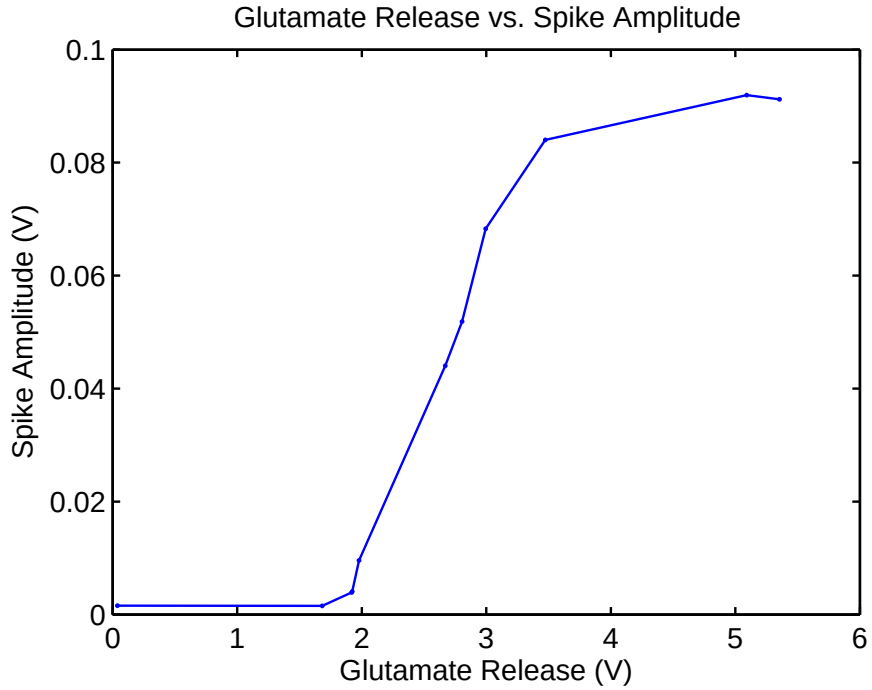

Fig.3 Spike amplitude as a function of the glutamate release level.

As shown in figure 3, the spike amplitude has a nonlinear relationship to the concentration of the glutamate release and this nonlinear pattern is concurred by experimental results (Popescu et al., 2004). Tiny amount of glutamate can not trigger any channel open. On the other hand, if the glutamate is above certain level, all the channel will be open and the curve is saturated.

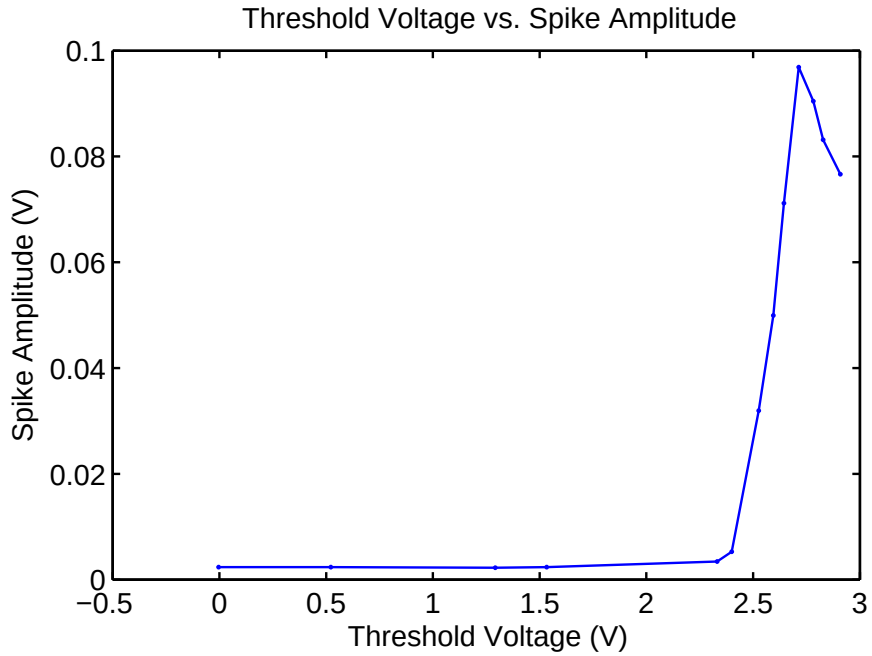

Fig.4 Spike amplitude as a function of the threshold voltage.

Shown in figure 4, we also investigated the effect of the threshold voltage to the spike amplitude. The nonlinear pattern and rational we propose here has also been raised before in experimental and theoretical studies (Jahr and Stevens, 1990a,b) . A very low or zero threshold voltage is analogous to a Mg^{2+} free extracellular medium and this will cause the channel to be open all the time. Shown in the plot, this is confirmed by no spikes in our circuit system since the membrane is discharged all the time. With the Mg^{2+} level increasing, the NMDA channel will have a higher chance of been blocked by it and less discharge for the membrane. This is shown in the graph as an rising spike amplitude with respect to the increasing Mg^{2+} level. Eventually, we are expecting to see the spike amplitude be stable at certain value when the Mg^{2+} level is high enough, because at this time, the NMDA channel should be almost blocked by the Mg^{2+} ions. But on the curve we see a small drop down of the voltage and this puzzle is still under study.

4 Discussion

To conclude, our project was initially motivated by the idea that biophysical models of neurons could be replicated on electronic circuit board. In this project, we finished design of a NMDA receptor that is regulated by its threshold voltage and glutamate release level. As was briefly mentioned in this report, the current mirror gives our circuit the ability to be connected as a network. We envision

this to be a valuable design and future works can put this circuit in parallel to achieve certain network functions such as Hebbian learning.

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