

Noisy Neurons

Hodgkin–Huxley Model and Stochastic Variants

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This article first reviews the basic concepts of the Hodgkin–Huxley model of nerve signal propagation. Recent experiments show fluctuations which call for introducing randomness into the model’s equations. Some simulations which reproduce the observed behavior are presented.

1. The Hodgkin–Huxley Model

A few billion years ago, life began. In its infant stages, life only manifested itself as unicellular organisms which did not have to tackle the problems of division of labour. Slowly though, as life evolved into more complex multicellular forms, diffusion and signal transduction which suffice for simple life forms, were not sufficient anymore and the need was felt for separate systems for transportation, signalling, respiration, etc. Hence, organisms evolved different organ systems devoted to different tasks, one of these being the nervous system which controls and instructs all other parts of the body.

The human nervous system has three basic parts: the brain, the spinal chord and nerves. The brain is the central controlling organ which sends instructions to all parts of the body via the spinal chord and nerves. The spinal chord is a bundle of nerve fibres which is responsible for quick responses to stimuli, i.e., reflexes. Nerves are fibres that conduct electrical signals and hence pass on information from and to the brain. Nerves are made of nerve cells called neurons (*Figure 1*).

Instructions in our body are sent via electrical signals that present themselves as variations in the potential across neuronal membranes. These potential differences

Keywords

Stochasticity, Hodgkin–Huxley, neurons, noise, differential equations.



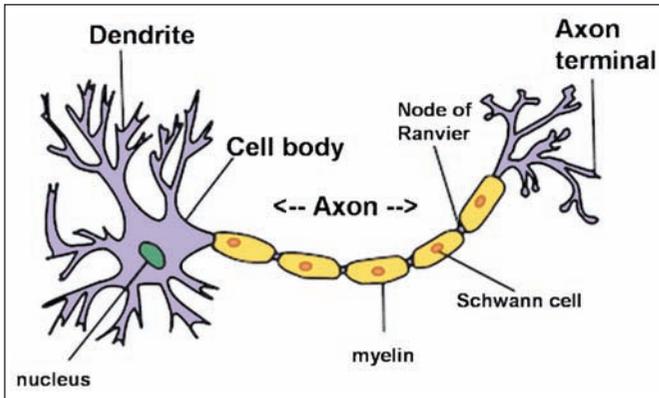


Figure 1. A schematic diagram of a neuron.

Source:

http://upload.wikimedia.org/wikipedia/commons/thumb/b/bc/Neuron_Hand-tuned.svg/400px-Neuron_Hand-tuned.svg.png

are maintained by ATP-dependent¹ ion pumps that fix the concentration of ions (mainly Na^+ and K^+) on either side of the membrane. An undisturbed membrane rests with a potential of about -70 mV across it. At this stage, all the ion channels (which are voltage-dependent) are closed.

Consider a hypothetical situation in which our body has no ions, excepting K^+ ions. If we open the K^+ ion channels at the resting potential, will there be a net flow of ions? Surprisingly, no. This is because the neuronal membrane is designed in such a way that its resting potential equals the equilibrium potential of K^+ ions. The definition of equilibrium potential becomes clear from the hypothetical situation above; it is the potential difference across a membrane at which the net flow of that particular ion across the membrane is 0.

The coinciding values of the K^+ equilibrium potential and the neuronal membrane resting potentials make sure that action potentials arise but do not persist. One must remember that the resting potential is not -70 mV because of the equilibrium potential of the K^+ ions. In fact, these potentials arise due to different reasons. The resting potential is maintained by ion-pumps and the K^+ potential is due to the EMF caused by the concentration difference.

¹ ATP stands for Adenosine Tri-Phosphate, the molecule which supplies energy to drive cellular processes such as ion pumps.



When a signal is sent, the potential across the membrane rises and if the potential crosses a threshold voltage (-30 mV), the Na^+ ion channels open. This leads to a sudden rise in potential towards the equilibrium potential of Na^+ . The Na^+ channels are open for a fixed time (about 1 ms). After that time period, the channels close. The K^+ channels, being on a slower time-scale, take more time to open and close. Thus, at about the time that the Na^+ channels close, the K^+ channels open forcing the potential (at a slower rate) back to the equilibrium potential of K^+ . Once the resting potential is reached, the K^+ channels take some time to respond and hence, the potential dips below the resting value before equilibrating at -70 mV (*Figure 2*).

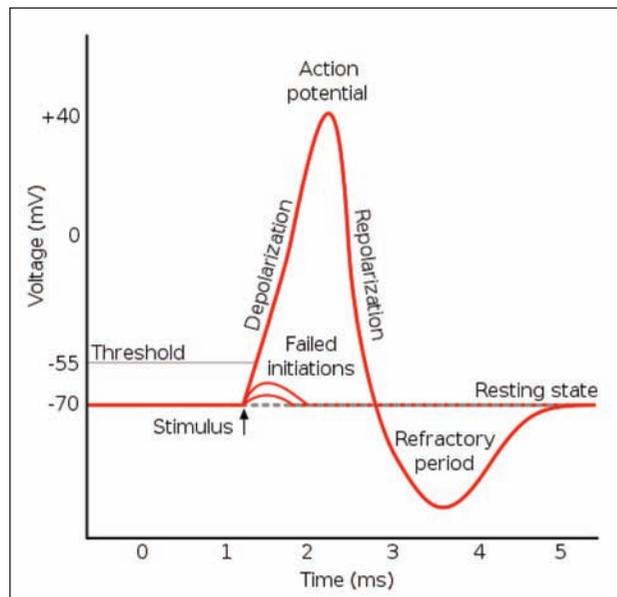
² If the absolute value of the potential crosses a certain value of voltage, the neuron will simply get 'fried'. Thus, here we consider only those values of potential which lie between biological limits.

During the period of inactivation of the Na^+ ion channels, no potential across the membrane, no matter how large², can set off an action potential. Thus, this period is called the refractory period. It is due to this that neuron conduction is unidirectional. An action potential can only go from the second neuron to the third because the first is in its refractory period.

Figure 2. A voltage vs. time graph of a neuron's membrane upon stimulation with a voltage greater than the threshold voltage.

Source:

<http://hmp physiology.blogspot.in/2012/10/membrane-and-action-potential.html>



Hodgkin and Huxley (1952) [1] visualised ion channels as having two contributors – a capacitor and a resistor. This suggested that the current across the ion channel would have two parts: a displacement current (i.e., the current charging the capacitor) and an ohmic current. Thus, they arrived at:

$$\frac{dV}{dt} = \frac{1}{C_M} (I - g_{Na}(V - V_{Na}) - g_K(V - V_K) - \bar{g}_l(V - V_l)) \quad (1)$$

Here, C_M is the capacitance of the membrane while g_{Na} , g_K and g_l are the respective conductivities of the Na^+ , K^+ and leakage ion channels and V_{Na} , V_K and V_l are the equilibrium potentials of Na^+ , K^+ and leakage ions respectively. The model builds in the following features:

- When the potential V equals any of the equilibrium potentials, the contribution of that channel to the current becomes 0 as it should, since at this voltage, the net flow of ions of that species across the membrane is 0.
- The equation includes a ‘forcing’ current I which is applied to the membrane. It then takes the net current to be the difference between I and the ion currents.
- dV/dt is equated to an I/C -type term – this follows from the basic equation relating the charge on a capacitor to the voltage.
- Leakage current is also incorporated. This accounts for ions that naturally permeate the membrane (not via the ion channels – hence the name ‘leakage’).

Hodgkin and Huxley now very cleverly introduced three variable n , m and h , which are connected to the conductances of the two ion channels as they govern the (probability of the) chemical interactions of the proteins forming the ion channels in response to voltage.

$$g_K(t) = \bar{g}_K [n(t)]^4, \quad (2)$$



$$g_{\text{Na}}(t) = [m(t)]^3 h(t) \bar{g}_{\text{Na}}. \quad (3)$$

One can think of these variables as gating variables which represent the probability of activation and inactivation of the ion channels. Indeed they are bounded between 0 and 1 and follow the dynamics:

$$\frac{di}{dt} = \alpha_i(1 - i) - \beta_i i, \quad (4)$$

where $i = n, m, h$.

Equations (1) and (4) form Hodgkin and Huxley's model for the fluctuation of voltage at one point of a membrane. They were very successful in explaining their experiments on the squid axon, and the equations have been used extensively since their Nobel Prize winning work.

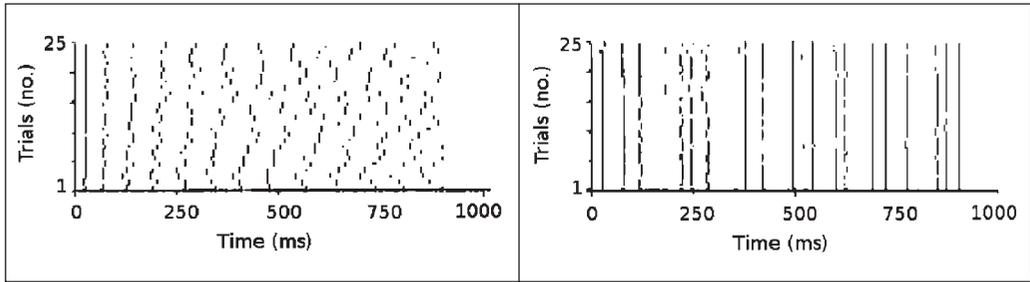
2. The Mainen–Sejnowski Experiment

In December 1994, Zachary F Mainen and Terrence J Sejnowski performed an experiment [2] on the neocortical neurons of a rat. There are two ways in which neurons can be studied. The first is the current–clamp mode in which the current across the neuronal membrane is kept fixed and the voltage is allowed to change. The second is the voltage–clamp mode in which the voltage across the membrane is fixed and the fluctuating current is measured. The neurons in this experiment were studied in the current–clamp mode.

As mentioned earlier, on applying a voltage more than the threshold voltage to the membrane, action potentials result. From (1), it is clear that a constant current of any non-zero value will lead to the production of a chain of action potentials.

Mainen and Sejnowski studied the spike timings of a neuron subjected to a constant current of 150 pA. They repeated this experiment 25 times and stacked their results to obtain the graph in *Figure 3*. It is clear that





constant current leads to coherent spike timings to begin with but becomes noisier and noisier as time progresses.

In the second part of their experiment, they subjected the neuron to a noisy current. Again, the experiment was repeated 25 times and the graph in *Figure 4* was obtained. The same noisy current was supplied to the cell each time, i.e., the graph of the current was identical each time. Also, note that the spike timings, though coherent, are not periodic.

Thus, the first part of the experiment showed that a constant current produces noisy spike timings and the second part showed the opposite.

3. Possible Models

Strangely, one shortcoming of the Hodgkin–Huxley model is its determinism – it has no random variables in it. Biological systems on the other hand, almost as a rule, are stochastic. Thus, the first thing we must try to do is to incorporate noise into our model in such a way that it captures the underlying stochasticity of the biology we are trying to model.

Let us look at the graph in *Figure 5*. It shows us how the probabilities n , m^3 and $1 - h$ of K^+ ion channel activation, Na^+ ion channel activation and Na^+ ion channel deactivation, respectively, change as time progresses. It now becomes clear why g_{Na} and g_K are represented as in (2) and (3).

Figure 3 (left). This is the first graph produced by the experiment. Here, we see that the neuron firing times get more and more uncorrelated as time progresses even though they start out coherently.

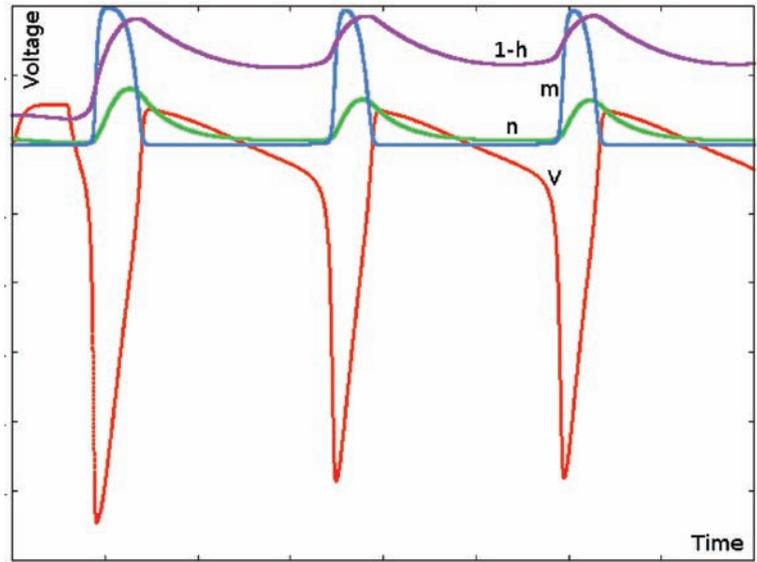
Source: From Zachary F Mainen and Terrence J Sejnowski, Reliability of spike timing in neocortical neurons, *Science*, New Series, Vol.268, No.5216, June 1995. Reprinted with permission from AAAS.

Figure 4 (right). This is the second graph produced by the experiment.

Source: From Zachary F Mainen and Terrence J Sejnowski, Reliability of spike timing in neocortical neurons, *Science*, New Series, Vol.268, No.5216, June 1995. Reprinted with permission from AAAS.



Figure 5. Changes in the probabilities n , m and $1-h$ (in green, blue and purple respectively) of K⁺ ion channel activation, Na⁺ ion channel activation and Na⁺ ion channel deactivation as time progresses. The voltage is shown in red.



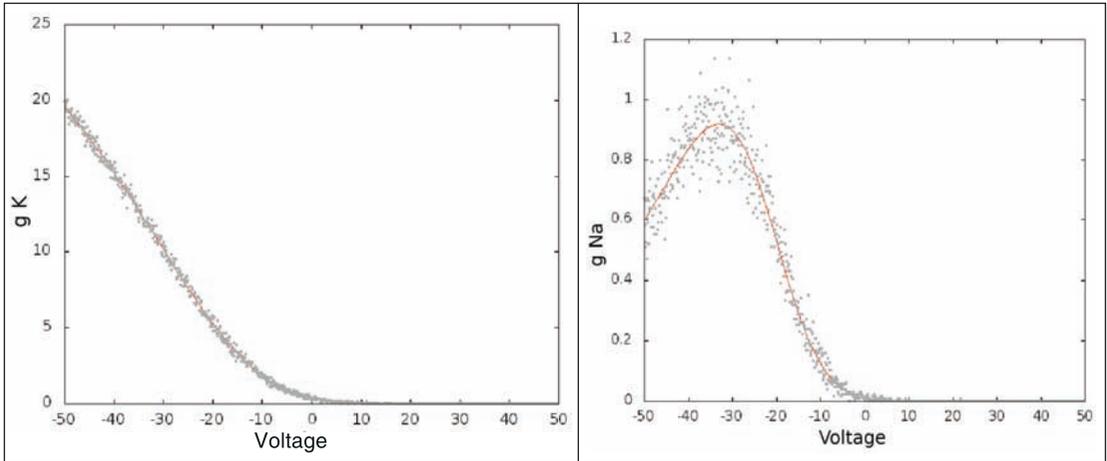
The values used in the simulations are $g_{\text{Na}} = 120$, $g_{\text{K}} = 36$, $g_{\text{l}} = 0.3$, $V_{\text{Na}} = -115$, $V_{\text{K}} = 12$, $V_{\text{l}} = 10.613$ and $C_{\text{M}} = 1$. The initial values used were $n = 0.444444444444$, $m = 0.122388497007$ and $h = 0.792611601759$.

The simplest way to model probability on the computer is to generate a uniform random number between 0 and 1. If it is less than a given probability $P(E)$, then event E is taken to occur in the simulation.

In the case of ion channels, one has to concentrate on some fixed area, say $100 \mu\text{m}^2$, count the number of K⁺ and Na⁺ ion channels present in that area and then run the simulation that many times. The results are shown in *Figures 6 and 7*.

When noise is added to the equation in this way, one will have to deal with a set of four coupled non-linear stochastic differential equations. If that doesn't sound intimidating, I don't know what does! Now the peculiarity of integrating white noise is that the second order terms, (which one normally ignores), play a role. Thus, to integrate a stochastic differential equation, one must





add a correction term known as the Wong–Zakai correction. On adding this correction term, the graph in *Figure 8* is obtained.

There are many other ways in which one can try to incorporate noise. From a purely mathematical perspective, one might even just add a Brownian term to the integrated expression for V . Other methods like neuronal tiring (by delaying response time to stimuli), using different methods of integration or using different kinds of

Figure 6 (left). Here we see the Hodgkin–Huxley prediction of the stable state of g_K for various values of V in red and the stable state of g_K calculated from simulations of the K^+ ion channels for various values of V in grey.

Figure 7 (right). Here we see the Hodgkin–Huxley prediction of the stable state of g_{Na} for various values of V in red and the stable state of g_{Na} calculated from simulations of the Na^+ ion channels for various values of V in grey.

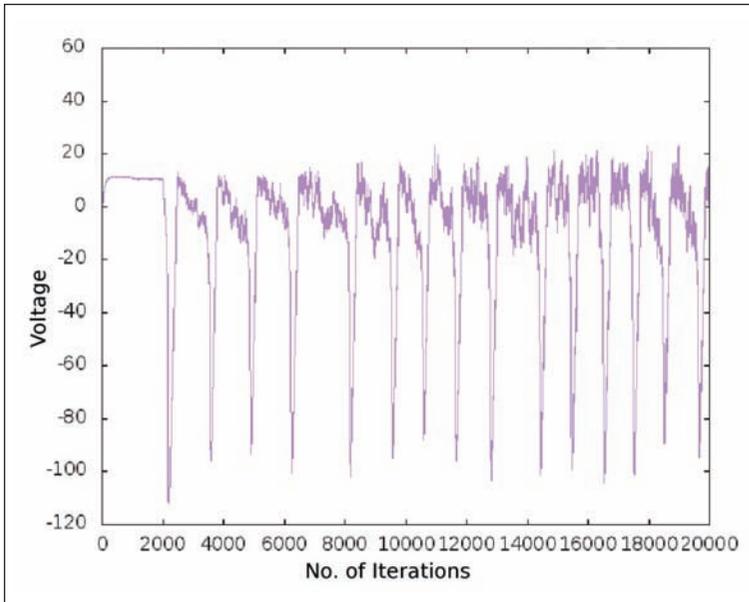


Figure 8. This is the graph obtained by applying the Wong–Zakai correction. We noticed that this is much noisier than any of the previous graphs that we obtained.



noise, have also been tried. The latter is not very useful for the prime reason that a sequence of random walks converges to Brownian motion. This justifies the use of Brownian motion as ‘integrated white noise’.

Another important method which was used was that of different time-scales. As mentioned earlier, the K^+ channels function on a much slower time-scale when compared with the Na^+ ones. Thus, one can run m and V on the faster time-scale with n and h on the slower one. But, with this method, one runs into very high run-times which become problematic to deal with.

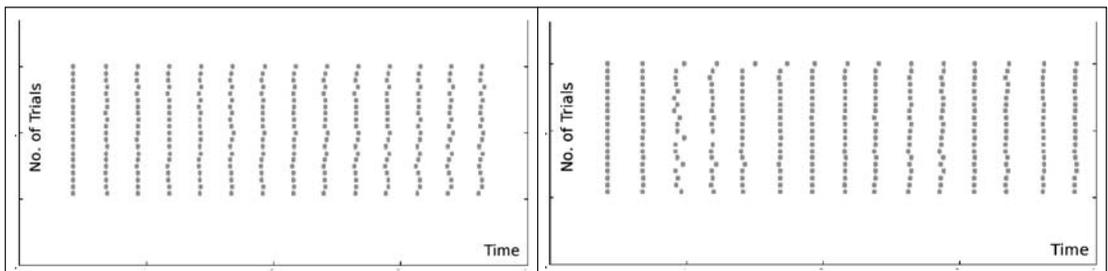
One universal problem in all these methods is that of initial conditions. The best way to kick-start the simulation is to let it run with $I = 0$ and $V = 0$ till it stabilises as in *Figure 5* and the other figures which have been generated.

Figure 9 (left). Stochasticity in the model has been introduced through the probabilities n , m^3 and $1-h$ of the (de)activation of the ion channels. The model was then run for a constant current.

Figure 10 (right). Stochasticity in the model has been introduced through the probabilities n , m^3 and $1-h$ of the (de)activation of the ion channels. The model was then run for a noisy current.

Among all these methods, the Wong–Zakai corrected ion channel simulation models give results that are closest to those in the Mainen–Sejnowski experiment. In *Figure 9*, the gradual onset of noise is apparent and in *Figure 10* other than two columns, the spike firings are perfectly coherent. Also, this model has the most sound biological backing and reasoning.

On a closing note, we would like to say that science advances by undoing all the approximations it has made. This leads us to deal with the incorporation of randomness and understanding emergence. It is through such problems that we will be able to understand the true nature of cells.



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Suggested Reading

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