Realistic Models of Neurons and Neuronal Networks

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This is an article that describes realistic models of neurons. The models range in complexity from the perfect integrate and fire model to conductance models in which the ionic currents are computed from the kinetics of the underlying gating particles.

1. Introduction

This section outlines the construction of neuronal models which describe in more detail their intrinsic properties as well as their interactions with neighbouring neurons. It starts with the integrate and fire neuron as a model on the less detailed end of the spectrum, while we finish with models in which the ionic currents emerge from the kinetics of the underlying gating particles. The complexity of the model chosen for a study would depend largely on the type of question being investigated. For example, one cannot fully investigate the effects of many drugs on a neuronal network without the use of the Hodgkin Huxley model. The reason being that in many cases, the effect of the drug is known in some detail e.g. benzodiazepines mostly effect the decay of γ-Aminobutyric acid A (GABA_A) mediated postsynaptic potentials and not the maximum conductance (Otis and Mody, 1992). On the other hand, if one is investigating auditory processing, there is already much which is unknown about the manner in which information is encoded in a simple network that constructing a complicated conductance model only serves to confound the problem. The extra details may also be irrelevant to the questions being addressed.

In describing various ‘realistic’ neuronal models starting out with the simplest, I will begin with the integrate and fire model. I will then move on to the leaky integrate
and fire model, the rate model of a neuron and finally conductance models. The conductance models can be constructed either with macroscopic descriptions of ionic currents or with more detailed models that outline the kinetics of each of the particles gating the channel. A study of network interactions requires models of synaptic activity. I will therefore describe two commonly used synaptic models – models with prefixed functions of postsynaptic activity and kinetic models. Finally since phenomena such as learning and memory require the investigation of neuronal plasticity, I present biological models of both short and long term plasticity.

2. Integrate and Fire Model

The integrate and fire model of neurons does not include any detailed information on the intrinsic properties of the neuron. Input to the neuron is integrated and a spike or action potential is generated once a fixed threshold is reached. The spiking property of the neurons allows for a study of the role of factors such as spike timing and spike synchrony in network activity. Some recent connectionist models incorporating the spiking activity of neurons have been found to yield certain advantages over a network of non-spiking neurons (Sougné, 1998). The integrate and fire neuronal model is described by the following type of equation:

\[ C_m \frac{dV_m}{dt} = I(t) \]  

\[ \text{(1)} \]

\( C_m \) is the capacitance of the neuron, \( V_m \) is the membrane potential and \( I(t) \) is the summated input current due to synaptic input from neighbouring neurons as well as any external current source such as an electrode. The neuron fires a fixed action potential when threshold is reached. The membrane potential is then set to a prefixed value after the spike. Implicit in such a model is the idea that the timing of a spike and not its form, is important in carrying information concerning the system.

The simplest way of representing a spike from the neuron is a simple delta function \( \delta(t-\tau_k) \) for a neuron which fires at time \( \tau_k \). While this is the simplest representation that can be used, various complications can be added to the model to more realistically characterise the neuronal spike and more importantly its activity immediately afterwards. Perhaps the most important of these is the refractory period immediately following an action potential. During this period no stimulus is able to elicit a second action potential from the neuron. The refractory period is due to the fact that the sodium channels largely responsible for generating a spike are in an inactivated state. The presence of this constraint places an upper limit on the frequencies at which a neuron may fire an action potential. If the refractory period is \( t_{\text{ref}} \), the maximum firing frequency of the neuron, \( f_{\text{max}} \) is \( 1/t_{\text{ref}} \). The neuronal model may also include a relative refractory period immediately following the refractory period during which the threshold for evoking a spike is increased.
3. Leaky integrate and fire model

These models add a new level of complexity in the behavior of a neuronal model by the inclusion of a leak current. The neuronal membrane in this instance can be represented by the equivalent circuit in Figure 1. The current flowing across the resistance of the circuit represents the leak current. The total current $I_m$ flowing across the neuronal membrane is the sum of the capacitance current $I_C$ and leak current $I_l$

\[
I_m = C_m \frac{dV_m}{dt} + \frac{V_m}{R_m}
\]  

(2)

The simple integrate and fire model would linearly integrate two temporally separated inputs provide their sum does not exceed threshold. The presence of a leak however introduces a more realistic behavior in which the occurrence of an input is gradually forgotten over time. The earlier occurring input therefore makes a less important contribution to the summated neuronal response at a latter time.

In the presence of a leak term, the membrane potential in the absence of any input current will gradually decay to its initial value. In response to a constant current pulse $I_m$, the leaky integrate and fire model would obtain the steady state value $V_m(\infty)=I_mR_m$. The value of the membrane potential before this steady state is reached however is given by

\[
V_m(t) = I_mR_m(1-e^{-t/\tau_m})
\]

(3)

Where $\tau_m=R_mC_m$ and is the membrane time constant representing the time taken for $V_m$ to reach 63% of its final value.

(4. Rate Model)

In many models of large networks, the neuronal output is not represented in the form of individual spikes. Instead the information taken into account is the firing rate of a neuron. In this case, the neuronal output is computed from a sigmoidal function relating membrane potential to the neuronal firing rate. The instantaneous firing rate $z_i(t)$ of a neuron is usually obtained from the neuronal membrane potential $V_m(t)$ with the use of a sigmoid function

\[
z_i(t) = \frac{z_{\text{max}}}{1 + e^{-b(V_m(t)-\theta)}}
\]

(4)

The use of this function allows for two factors contributing to nonlinearities in the neuronal output. Due to the refractory period, there is a maximal rate at which the neurons can fire $z_{\text{max}}$. The second factor is a threshold to reflect the fact that a minimum
excitation is required for the neuron to begin firing. The factors $b$ and $\theta$ contribute to setting the threshold of excitation and also the rate at which the firing increases with membrane potential.

The use of a rate model of course does not allow for the use of information that might be represented in the timing of neuronal firings or the correlation of firing times between neurons. The question of whether a rate code or temporal code is used for information coding in the nervous system has been a very active one for the last few years. Among the investigators who have presented evidence for the representation of stimulus information in the temporal modulation of the neuronal spike train have been Bialek et al (1991) who worked in the visual fly system and Richmond et al (1987) who investigated the inferior temporal cortex. The stance that spike timing in neuronal firing is not very important has been taken by investigators such as Shadlen and Newsome (1998) and Thomas et al (2000). The latter investigators present evidence to demonstrate that a good level of category information can be represented in the inferior temporal cortex without information concerning spike timing.

5. Synaptic input to the integrate and fire neuron

When present in a network, the neurons receive input from the surrounding neurons. At a given time step all the input from the surrounding neurons are summed linearly to give the resulting activity $V_i$ of a neuron $i$

$$C_m \frac{dV_i}{dt} = \frac{V_i}{R_m} + \sum_j \sum_k \omega_{ij} g_{ij} (t - \tau_k) \delta_j (t - \tau_k) [V_i - V_{eq}]$$ \hspace{1cm} (5)

The double summation is to take into account not only the input from all the presynaptic neurons $j$, but also to sum over each incidence $k$ of a presynaptic neuron firing. The term $\omega_{ij}$ is the sign and the strength of connections between neurons $i$ and $j$. The function $g_{ij}(t-t_0)$ usually takes the form of an alpha function

$$g_{ij} (t-t_0) = \frac{(t-t_0)}{\tau} e^{-\frac{(t-t_0)}{\tau}}$$ \hspace{1cm} (6)

Where $t_0$ is the time of transmitter release. The function $g_{ij}(t-t_0)$ decays with a time constant $\tau$ after reaching a peak. The values of $\tau$ are chosen to reflect the various fast and slow excitatory and inhibitory synapses seen in the nervous system. In many realistic network models these include the fast inhibitory synapse GABA$_A$, the slow inhibitory synapse GABA$_B$, fast excitation mediated by amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) receptors and a slow excitation mediated by N-methyl-D-aspartate (NMDA) receptors. Each synapse also has its own characteristic value of $V_{eq}$ where $(V-V_{eq})$ represents the driving force on each synaptic current.
6. Conductance models

Many studies in Neuroscience involve an investigation of the neuronal ionic channels. The effects of various drugs on neurons are understood in terms of their actions on the ionic channels. The framework primarily used to describe these channels is the Hodgkin Huxley model (1952). One of the principle advantages of using this model is the availability of a large number of the required parameters from the experimental literature. This is because many of the experimental investigations themselves are carried out using the Hodgkin Huxley framework. Some of the disadvantages of using the model is the large number of parameters required to characterize the system and the long computer run times required to treat such unwieldy systems.

Ionic channels in the Hodgkin Huxley model are represented as resistances (or conductances) arranged in parallel (Figure 2). The equivalent circuit for such a system is an elaboration of what has already been presented in Figure 1. In this case additional resistances are added to simulate the other currents in the neuronal membrane in addition to the leak current. The circuit in Fig 2 represents the currents that are typically represented in models of thalamocortical (TC) cells (Lytton and Thomas, 1997; Thomas and Lytton, 1997; Thomas and Grisar, 2000). The equation which describes such a circuit is the following

\[
C_m \frac{dV}{dt} = -I_T - I_h - I_{Na} - I_K - I_l - I_{GABA_A} - I_{GABA_B}
\]

(7)

The currents \(I_T, I_h, I_{Na}, I_K\) and \(I_l\) are intrinsic currents while \(I_{GABA_A}\) and \(I_{GABA_B}\) are synaptic currents. The values of these ionic currents are obtained from Ohm’s law

\[
I = g \bar{g}(V - E_{eq})
\]

(8)

\(E_{eq}\) is the reversal potential of the channel and \(\bar{g}\) is the maximum conductance of a channel. Both these values are fixed. The value of \(g\), the channel conductance, on the other hand is frequently dependent on things such as the membrane potential, time, or the internal calcium concentration and has to be generally computed for each channel at each time step. The leak current is usually an exception to this.

In the case of the intrinsic channels in which \(g\) changes, the value of \(g\) depends on the state of the gating particles \(m\) and \(h\). While \(m\) is an activation gate, \(h\) is an inactivation gate. If \(N\) is the number of activation gates

\[
g = m^N h
\]

(9)

The state of the gating particles (\(m\) or \(h\)) is a function of membrane potential as well as time. At any time \(t\), its value can be computed from the equation
The values $gate_a$ and $\tau_{gate}$ depend on membrane potential. In the case of many channels, their values as a function of membrane potential is directly available from experimental literature.

In other cases they have to be computed from $\alpha$ and $\beta$, the rate constants for the reaction between open and closed states for gating particles

$$gate_{open} \xrightarrow{\alpha} \xleftarrow{\beta} gate_{closed}$$

(11)

In this case

$$gate_a(V) = \frac{\alpha(V)}{\alpha(V) + \beta(V)}$$

(12)

$$\tau_{gate}(V) = \frac{1}{\alpha(V) + \beta(V)}$$

(13)

As indicated by the name, the value $gate_a$ determines the magnitude of gate opening when the membrane potential is held at a particular value for time infinity. The value of $\tau_{gate}$ determines the amount of time required for the gate opening.

(Approximate position of figure 2)

7. Kinetic models of ionic channels

The Hodgkin and Huxley representation of ionic currents is one at a macroscopic level. Many models also portray the currents at a more detailed level by describing the ionic channel based on the state transitions of each of the gating particles that constitute the channel. The value of an ionic current therefore emerges from the underlying dynamics of the system. There are two key assumptions that underlie classical kinetic theory which is used to describe the state transitions of the gating particles 1) Gating is a Markov process i.e. the rate constants of the transition of a gating particle from one state to the other (eg open to closed) is independent of the previous history of the system. 2) The transitions can be described by first order differential equations with a single time constant.

A construction of such models can be illustrated by the model of a potassium (K) channel previously described by Hodgkin and Huxley. The channel is made up of 4 $n$-gates. Each of these gates can be in either an open (1) or closed (0) state. The channel is only conducting if all four $n$ gates are in an open state (1111). Starting from the
condition where all the gates are closed (0000), the system can therefore go through 14 intermediate closed states before finally becoming open (1111) (Figure 3). By using the assumption that the four gates are independent and kinetically identical, the web of equations that lead from the non-conducting to conducting state of the K ionic channel can be very much reduced. For example all states with the same number of closed gates are kinetically identical and can therefore be treated together. Using such assumptions the entire tree of reactions can be collapsed to the transitions between 5 major states, with state 4 being the only conducting state. The values $4\alpha$, $3\alpha$, $2\alpha$, $\alpha$, are the rate constants for all the forward reactions leading to state 4, while $4\beta$, $3\beta$, $2\beta$ and $\beta$ are the rate constants for the backward reactions leading from open state 4 to the closed state 0. (approximate position of figure 3)

8. Synaptic input to conductance models

Synaptic input in many conductance models is represented in the form of the alpha function introduced in Section 5. As mentioned earlier, one of the problems with the use of this model is the fact that the time of occurrence of each spike has to be stored in a queue and their corresponding exponentials have to be calculated for each time step. Another criticism of these models is that while they imitate the observed time course of postsynaptic potentials in electrophysiological recordings, they are not based on any of the underlying mechanisms in the process. These models also do not naturally provide for a saturation that could occur at the synapse.

A kinetic model of receptor binding described by Destexhe et al (1994a) is able to resolve many of these problems. In a two state kinetic model, neurotransmitter molecules T, bind to the postsynaptic receptor R according to the first order scheme

\[
R + T \xrightarrow{\alpha} TR^* \xleftarrow{\beta} R + T
\]  

If $r$ is the fraction of bound receptors, then

\[
\frac{dr}{dt} = \alpha[T](1 - r) - \beta r
\]  

If $[T]$ occurs as a pulse, the above equation can be solved to obtain the following expression for the value of $r$ during the pulse ($t_0 < t < t_1$) and for the period following the pulse ($t > t_1$).

During the pulse

\[
r(t - t_0) = r_\infty + (r(t_0) - r_\infty)\exp\left[-\frac{(t - t_0)}{\tau_r}\right] \quad (t_0 < t < t_1)
\]  

After the pulse
\[ r(t - t_i) = r(t_i) \exp[-\beta(t - t_i)] \quad (t > t_i) \]  
(17)

Where both \( r_\infty \) and \( \tau_r \) are functions of the rate constants \( \alpha \) and \( \beta \) of equation 14.

The value of \( r \) is then used to calculate the synaptic current in the same manner as an intrinsic current.

\[ I_{\text{syn}}(t) = g_{\text{syn}}r(t)[V_{\text{syn}}(t) - E_{\text{syn}}] \]  
(18)

While these two state models capture many of the important characteristics of postsynaptic potentials, a larger number of states can be used to more accurately model them (Destexhe et al, 1994b).

9. Models of synaptic modification

The efficacy of connections between the neurons of the nervous system has been found to be a parameter which is not constant but fluctuates based on the dynamics of the network. These changes can be both long and short term and can cause synaptic efficacy to increase or decrease. While the short term changes last on the order of seconds to minutes, the long term changes can persist for an hour or more.

A model for short term synaptic facilitation and depression has been provided by Abbott et al (1997). In this model, the amplitude of neuronal response \( K_1 \) is adjusted by a factor \( A(t_i) \). If \( R \) is the response of a neuron to a train of spikes

\[ R(t) = \sum A(t_i)K_1(t-t_i) \]  
(19)

If there was an isolated spike and previous spikes did not have an influence on the postsynaptic response, \( A \) would have the value 1. As a result of a presynaptic spike however, \( A \) would either increase in the case of facilitation or decrease in the case of depression. This could either take place in an additive or multiplicative fashion. The value of \( A \) would change according to \( A+fA \) in the multiplicative case or \( A+A+(f-1) \) in the additive case. A value of \( f>1 \) would correspond to facilitation while \( f<1 \) would lead to depression. In order to produce biologically realistic behavior, Abbott recommends the usage of a multiplicative expression for depression \( (f<1) \) and an additive description for facilitation \( (f>1) \).

Another model of short term depression can be found by Markram et al (1998). This model aims to explain the frequency dependence of synaptic transmission. Both Markram and Abbott have suggested that these changes in synaptic strength have implications for the sort of encoding used by the nervous system. A rate code is favored when depressions is slow and a temporal code when depressions is fast. A neuron which was initially sensitive to the firing rate of a rapidly firing presynaptic terminal, as a result of synaptic depression, now reaches a steady state which is no longer a function of presynaptic firing rate. Several depressed EPSP’s however are generated before this steady state is reached. During this period, the neuron shows an increased sensitivity to

The long term changes observed in the strengths of synaptic connectivity are long term potentiation and long term depression. The experimental paradigm usually used to produce LTP is a train of high frequency stimulation while LTD is produced by a train of low frequency stimuli. LTP has found to be mediated by both NMDA as well as non-NMDA synapses. Long term potentiation mediated by NMDA synapses generally obey Hebbian rules for induction. The Hebbian rule was proposed by Donald Hebb as a mechanism for learning. He proposed that the concurrent excitation of pre and postsynaptic elements would result in an increase of synaptic efficacy. In the NMDA synapse the requirement for concurrence arises because the postsynaptic terminal has to be depolarized in order to remove a \( \text{Mg}^{2+} \) block. The presynaptic terminal has to be depolarized for the release of neurotransmitter. Realistic models of the NMDA synapse must therefore take into account the concentration of \( \text{Mg}^{2+} \). The following is an example of an equation for an NMDA mediated current in a model of working memory in the cortical network (Wang, 1999)

\[
I_{\text{NMDA}} = \frac{g_{\text{NMDA}}(V_m - V_E)}{(1 + [\text{Mg}^{2+}]e^{-kV_m})} \quad (20)
\]

More recent experimental work has revealed more details on how the relative timing of pre and postsynaptic firing can change the sign as well as the strength of synaptic modification. If the presynaptic action potential precedes postsynaptic firing by no more than about 50ms, then an increase in synaptic strength takes place. The smaller the temporal separation between the timing of the presynaptic firing and the postsynaptic action potential, the larger the increase in synaptic strength. On the other hand, presynaptic action potentials that follow postsynaptic spikes lead to a depression in synaptic strength. Models of this sort of spike timing dependent plasticity have been developed by Song et al (2000).

10. Multicompartmental models

The highly branched dendritic trees of a neuron confer a highly complex spatial structures to the neuron. Neuronal models which attempt to understand the role of these structures make use of multicompartmental (figure 4). The compartmental approach to study the flow of ionic currents in dendritic trees, was pioneered by Rall (1964). Rall had modeled the dendritic tree with the use of cable equations. These equations could be analytically solved under extremely limited circumstances. This approach became difficult and sometimes impossible when most realistic dendritic structures were taken into account. Also problematic are membrane properties which are voltage dependent and which generate action potentials. Rall had pointed out that in such cases, compartmental models should be used. A good description of such models can be found in Segev and Burke (1999). In this instance each neuron is made up of a number of compartments. Each compartment is considered isopotential and its properties to be uniform. For such models, the property of each compartment is not only the consequence
of currents intrinsic to the compartment but also depend on currents which enter and leave from adjacent compartments.

The membrane potential for a neuronal compartment $k$ with adjacent compartments $k+1$ and $k-1$ is then computed as follows

$$ c_m \frac{dV_k}{dt} + I_{ion} = \frac{V_{k-1} - V_k}{r_{k-1,k}} - \frac{V_k - V_{k+1}}{r_{k,k+1}} $$

(21)

While in many instances, unicompartment models are sufficient to generate the activity of interest, in some situations, they fail. An example of this is a study described by Abbott and Marder (1998). They demonstrate how in some bursting cells in the somatogastric ganglion of certain invertebrates, it is important to isolate the primary neurite from the spike initiation zone on the axon. If this is not done, the slow oscillating potentials generated in the primary neurite can prevent the deinactivation of the fast Na+ conductance which terminates the action potential in the spike initiation zone. Once these two areas are electrotonically separated, the problem is resolved.

(Approximate position of figure 4)

References


**Glossary**

Integrate and fire neuron model – neuronal model in which neuron integrates all input and fires when threshold is reached.

Leaky integrate and fire neuron model – neuronal model in which the neuron gradually ‘forgets’ earlier inputs due to the presence of a leak current.

Rate model – non-spiking model of neuron in which firing rate of neuron is usually computed from a sigmoid function of neuronal membrane potential.
Kinetic models of channels – Models of intrinsic neuronal or synaptic channels in which the channel currents are computed from the kinetics of the particles which constitute the channel.

Conductance model – neuronal model in which the various ionic channels of a neuron are represented as the resistors in an equivalent circuit

Equivalent circuit – model of neuronal activity in terms of electrical components such as resistors and capacitors

Synaptic plasticity – alterations in the efficacy of a synapse. These changes may be positive or negative and they can be of both short and long term durations.

Further reading


Figure Legends

Figure 1 Equivalent circuit for model of leaky integrate and fire model neuron
Figure 2 Equivalent circuit for conductance model of thalamocortical neuron

Figure 3 a) The K channel consisting of 4 \( n \) particles can go from the closed state (0000) to the only open state (1111) via 14 intermediate states which are all closed. b) By lumping together states which are kinetically identical, the complex state diagram in a) can be reduced to 5 states (Hille, 1991).

Figure 4 Equivalent circuit for multicompartment model (Segev and Burke, 1999)
Figure 4. Equivalent circuit for multicompartment model (Segev and Burke, 1999).
Figure 3 a) The K channel consisting of 4 \( n \) particles can go from the closed state (0000) to the only open state (1111) via 14 intermediate states which are all closed. b) By lumping together states which are kinetically identical, the complex state diagram in a) can be reduced to 5 states (Hille, 1991).
Figure 2. Equivalent circuit for conductance model of thalamocortical neuron.
Figure 1. Equivalent circuit for model of leaky integrate and fire model neuron.